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ESSENTIAL NOTES IN PAIN MEDICINE

Edited by
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Essential Notes in
Pain Medicine

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Enrique—Dedicated to my wife Alix, our son Henry, and to our family

Alifia—To my husband Mustafa and our boys Zuhair and Zayaan; this could not have been possible without your support

Jan—Dedicated to my wife Tugba and my sons Deniz, Bernhard, and Albrecht

Foreword

The practice of clinical medicine across its various specialties has much in common. It includes at its core patient communication to obtain valid information and to optimize compliance with treatment, consideration of diagnostic probabilities through history, examination, and investigations, and treatment delivery either directly or by referral. These skills are learnt by apprenticeship but, even in the information age, require a substantial body of knowledge to be drawn upon that is wide-ranging. The latter is tested through examination by the governing bodies that regulate postgraduate medical training, and the relatively new specialty of pain medicine has followed suit with fellowship examinations across the world. This book on pain management provides a wide-ranging and detailed overview of topics that would appeal to the examination candidate in need of a summary prior to their sitting of fellowship pain examinations.

The book assumes a background knowledge, but in areas where the reader feels they are limited in this, then references to background sources are provided. The subject is covered in its breadth, ranging from basic sciences underpinning the subject to clinical matters of assessment tools and treatment. Being a book for the trainee sitting examinations, it also includes those rarities oft favoured by examiners to assess clinical acumen and logical thought, but also includes, amongst these, some that will, on occasion, arise in a long career that follows, for example, serotonin syndrome, glossopharyngeal neuralgia, and refractory angina, to name but a few. As such, this book would also appeal to the pain clinician in practice, especially at the start of their career.

In providing such a broad overview, it allows the reader to not only look up matters for reminder of detail such as drug prescription, but also be aware of the treatment options, from which they can consider whether to refer on or obtain further information and apprenticed training to pursue these themselves.

The book provides a summary of pain as a psychophysical phenomenon by including details on physiology and psychology. From this flows the philosophy for assessment and management, and thus this book not only is an aide memoire for examinations, but it also provides an anchor for a clinician's ongoing career with the challenges of new information on current treatments, as well as new treatments to be subsequently appraised in the context of a paradigm for pain management.

The multiauthor book, while drawing predominantly on UK physicians, also includes several from other countries and, in so doing, provides a broad approach. Furthermore, the authorship includes those with excellent and innovative practices, some of whose work is not widely appreciated and whose ideas may offer appealing ways to develop a practice, with some examples being the use of steroid passports, how to write a patient letter, and examination signs of opioid dependence.

Much of pain practice involves the elderly, rheumatological conditions, and psychological problems and all of these are addressed in some depth and will serve the pain physician well.

I congratulate the editors on bringing this broad and skilled authorship together and offering a concise book for the benefit of examination candidates and early career pain physicians.

Jon Raphael
Professor of Pain Science, Birmingham City University

Preface

'Your pain is the breaking of the shell that encloses your understanding' – Khalil Gibran
From *The Prophet* (Knopf, 1923)

Pain is an unpleasant and emotional experience, but it is not just for the person suffering from it, but also for loved ones. It remains underestimated and undertreated, and has a major impact in our society. Treatment for alleviation of pain has been present since the dawn of mankind and has continued to evolve. Various initiatives have been introduced to make pain a priority, as it is one of the most common symptoms with which patients present to general practitioners and hospitals.

In 2012, the Faculty of Pain Medicine of the United Kingdom (UK) introduced the exam for the Fellowship in Pain Medicine (FFPMRCA). We were amongst the first anaesthetists with an interest in pain medicine, sitting this written and oral exam in the UK. With our collective knowledge, skills, and experience, we initially decided to write a book with a collection of relevant questions and answers which would have benefitted mainly the pain fellows and trainees sitting the pain exam. The format of the book was changed to serve as a comprehensive collection of high-quality resources written by various health care professionals, with an interest in pain medicine. It is based on the curriculum of the pain medicine fellowship exam in the UK, including relevant topics, which are vital for pain clinics, interventional procedures, and allied health therapies.

The book will help all pain doctors and medical and allied health care specialists who treat inpatient and outpatient chronic non-cancer and cancer pain patients, as well as pain trainees and fellows who are subspecializing in pain medicine. It will also be an excellent resource for candidates preparing for postgraduate examinations in pain medicine in the UK and/or other countries, as well as for postgraduate examinations of specialist colleges where pain medicine is in the curriculum such as rheumatology, neurology, sports medicine, addiction medicine, general practice, psychiatry, occupational therapy, rehabilitation, surgery, and other specialties.

The chapters have been organized into nine sections, commencing with pain assessment, through physiology, pharmacology, relevant pain interventions, clinical conditions associated with pain, psychological impact, and its multidisciplinary management, along with sections on cancer pain and epidemiology/evidence-based medicine.

We are extremely grateful for the expertise and hard work of our contributors and specialists from all over the world for their continued support and professionalism to make this book a success in providing an excellent and concise overview over the whole spectrum of pain medicine.

We hope that the readers of this book find it useful not only for their exams, but also as a comprehensive and suitable reference guide in their clinical practice, to improve the quality of care we provide to our patients.

Acknowledgements

We are very obliged to have had a fantastic team of authors who have contributed towards this book. Thank you for your precious time, patience, and commitment, while accommodating multiple requests for changes and amendments along the way. It has been a great pleasure working collaboratively with you all.

To write and edit a book is a complex task and has been a great educational experience for us. We could not have achieved this without the invaluable and fantastic support from Rachel Goldsworthy, Geraldine Jeffers, and Fiona Sutherland, from Oxford University Press, and Helen Nicholson from Newgen Publishing UK who have tirelessly helped us through this journey.

Last, but not the least, we are particularly grateful to our families for their constant encouragement, backing, and tolerance during the last few years, thank you!

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Abbreviations

1st ON	first-order neuron
2nd ON	second-order neuron
3rd ON	third-order neuron
AA	arachidonic acid
AACP	Acupuncture Association of Chartered Physiotherapists
AAGBI	Association of Anaesthetists of Great Britain and Ireland
ACDF	anterior cervical discectomy and fusion
ACEI	angiotensin-converting enzyme inhibitor
acetyl-CoA	acetyl coenzyme A
ACh	acetylcholine
ACJ	acromioclavicular joint
ACPA	anti-citrullinated protein antibodies
ACT	acceptance and commitment therapy
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
ADL	activities of daily living
ADRB	aberrant drug-related behaviour
AHCPR	Agency for Health Care Policy and Research
AIDS	acquired immunodeficiency syndrome
ALARP	as low as reasonably practical
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor
ANA	anti-nuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
ANOVA	analysis of variance
ANS	autonomic nervous system
AP	action potential; anteroposterior
ARDS	acute respiratory distress syndrome
ARR	absolute risk reduction
ASA	American Society of Anesthesiologists
ASIS	anterior superior iliac spine
ATLS	Advanced Trauma Life Support
ATP	adenosine triphosphate
AV	atrioventicular
BA	bioavailability
BAcC	British Acupuncture Council
BAI	Beck Anxiety Inventory
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BBB	blood–brain barrier
BDNF	brain-derived neurotrophic factor
BiPAP	bilevel positive airway pressure
BMAS	British Medical Acupuncture Society
BMD	bone mineral density
BMI	body mass index
BMS	burning mouth syndrome
BNF	British National Formulary
BP	blood pressure
BPI	Brief Pain Inventory
BTX-A	botulinum toxin type A
BTX-B	botulinum toxin type B
BZD	benzodiazepine
Ca^{++}	calcium
CABG	coronary artery bypass grafting
cAMP	cyclic adenosine monophosphate
CBD	cannabidiol
CBG	corticosteroid-binding globulin
CBN	cannabinol

CBR cannabinoid receptor
CBT cognitive behavioural therapy
CCP cyclic citrullinated peptide
CDA cervical disc arthroplasty
cDMARD conventional disease-modifying anti-rheumatic medication
CFS chronic fatigue syndrome
CFT compassion focused therapy
CGRP calcitonin gene-related peptide
CHEOPS Children's Hospital of Eastern Ontario Pain Scale
CI confidence interval
CINV chemotherapy-induced nausea and vomiting
CK creatinine kinase; creatine kinase
Cl clearance
CMT Charcot–Marie–Tooth
CMV cytomegalovirus
CN cranial nerve
CNCP chronic non-cancer pain
CNMP chronic non-malignant pain
CNS central nervous system
CO_2 carbon dioxide
COMT catechol-O-methyltransferase
CONSORT Consolidated Standards of Reporting Trials
COPD chronic obstructive pulmonary disease
COX cyclo-oxygenase
CPAP continuous positive airway pressure
CPAQ Chronic Pain Acceptance Questionnaire
CPB coeliac plexus block
CPM conditioned pain modulation
CPR cardiopulmonary resuscitation
CPSP chronic post-surgical pain
CRF corticotropin-releasing factor
CRH corticotrophin-releasing hormone
CRP C-reactive protein
CRPS complex regional pain syndrome
CSCI continuous subcutaneous infusion
CSF cerebrospinal fluid
CSP Chartered Society of Physiotherapy
CSQ Coping Strategies Questionnaire
Css plasma concentration at steady state (mg/mL)
CT computed tomography
CVS cardiovascular system
CXR chest X-ray
CYP cytochrome peroxidase
CYP450 cytochrome P450 isoenzymes
CYP2C9 cytochrome P450 2C9
CYP3A4 cytochrome P450 3A4
DAG diacylglycerol
DAP dose–area product
DASS Depression, Anxiety, and Stress Scale-21
DBS deep brain stimulation
DBT dialectical behaviour therapy
DCT distal convoluted tubule
DEXA dual-energy X-ray absorptiometry
DH dorsal horn
DLPFC dorsolateral prefrontal cortex
DMSO dimethylsulfoxide
DMT disease-modifying therapy
DN4 douleur neuropathique 4
DNA deoxyribonucleic acid
DOP delta opioid
DRG dorsal root ganglion
DSA digital subtraction angiography
dsDNA double-stranded DNA
DSM-5 Diagnostic and Statistical Manual of Mental Disorders, fifth edition
DS-SAT Discomfort Scale-Dementia of Alzheimer Type
DVLA Driver and Vehicle Licensing Agency
DVT deep vein thrombosis
EAR estimated average requirement
EBM evidence-based medicine
ECG electrocardiogram
ECSWT extracorporeal shockwave therapy
ED50 effective dose 50
EDS Ehlers–Danlos syndrome
EDTA ethylenediaminetetraacetate
EEG electroencephalogram
EF ejection fraction
eGFR estimated glomerular filtration rate
EMG electromyography, electromyelogram

EN-PNS	external peripheral nerve stimulation
ENT	ear, nose, and throat
EO	external oblique
EPSP	excitatory post-synaptic potential
EQ-5D	EuroQol-5D
ERCP	endoscopic retrograde pancreaticocholangiography
ESI	epidural steroid injection
ESR	erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FABQ	Fear Avoidance Beliefs Questionnaire
FAIR	flexion, adduction, and internal rotation
FBC	full blood count
FBSS	failed back surgery syndrome
FDA	Food and Drug Administration of the United States
FDG-PET	fluorodeoxyglucose positron emission tomography
FHR	fetal heart rate
FLACC	Face, Legs, Activity, Cry, and Consolability (Scale)
FLAIR	fluid-attenuated inversion recovery
fMRI	functional magnetic resonance imaging
FN	false negative
FP	false positive
FPS-R	Faces Pain Scale-Revised
FRP	functional restoration programme
FSH	follicle-stimulating hormone
G	Gauge
G-6-PD	glucose-6-phosphate dehydrogenase
GABA	gamma aminobutyric acid
GABA-T	GABA-transaminases
GAD	glutamic acid decarboxylase
GAD-7	Generalized Anxiety Disorder-7
GAT	GABA transporter
GC	glucocorticoid; grey commissure
GDNF	glial cell line-derived neurotrophic factor
GDS	Geriatric Depression Scale
GET	graded exercise therapy
GFN	genitofemoral nerve
GFR	glomerular filtration rate
GHQ	General Health Questionnaire
GI	gastrointestinal
GMI	graded motor imagery
GON	greater occipital nerve
GP	general practitioner
GPCR	G-protein coupled receptor
GPM	Geriatric Pain Measure
GWAS	genome-wide association studies
H^+	proton
HADS	Hospital Anxiety and Depression Scale
Hb	haemoglobin
HDU	high dependency unit
5-HIAA	5-hydroxyindoleacetic acid
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
H_2O PET	water-based positron emission tomography
HPA	hypothalamic–pituitary–adrenal
HPPH	5-(p-hydroxyphenyl)-5-phenylhydantoin
HR	heart rate
5-HT	5-hydroxytryptamine (serotonin)
IA	intrinsic activity
IAPT	Improving Access to Psychological Therapies
IASP	International Association for the Study of Pain
IBS	irritable bowel syndrome
ICP	intracranial pressure
ICD-11	International Classification of Diseases, 11th Revision
ICU	intensive care unit
IFN-γ	interferon gamma
Ig	immunoglobulin
IgA	immunoglobulin A
IHD	ischaemic heart disease
IHN	ilio-hypogastric nerve
IIm	internal intercostal membrane
IIN	ilio-inguinal nerve
IL	interleukin
IM	intramuscular
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IN-PNS	internal peripheral nerve stimulation
INR	international normalized ratio
IO	internal oblique

IP3	inositol triphosphate
IPT	inpatient pain team
IQ	intelligence quotient
IQR	interquartile range
IR	immediate release
IRAS	Integrated Research Application System
IRMER	Ionising Radiation (Medical Exposure) Regulations
ISSVD	International Society for the Study of Vulvovaginal Disease
IT	intrathecal
ITDD	intrathecal drug delivery
IV	intravenous
JIH	joint hypermobility syndrome
K^+	potassium
Ke	elimination rate constant (min^{-1})
KOP	kappa opioid
LA	local anaesthetic(s)
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LASER	light amplification by stimulated emission of radiation
LET	linear energy transfer
LFT	liver function test
LH	lateral horn; luteinizing hormone
LLLT	low-level laser therapy
LON	lesser occipital nerve
LSD	lysergic acid diethylamide
LTP	long-term potentiation
MAC	minimum alveolar concentration
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitors
MAPK	mitogen-activated protein kinases
MBB	medial branch block
MBSR	mindfulness-based stress reduction
MCBT	mindfulness-based CBT
mcg	microgram (μg)
MCP	metacarpophalangeal
MCS	motor cortex stimulation
MD-2	myeloid differentiation protein 2
MDMA	3,4-methylenedioxy-methamphetamine
MDT	multidisciplinary treatment
ME	myalgic encephalomyelitis
MEG	magnetoencephalography
Mg^{++}	magnesium
MHD	monohydroxy derivative
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction; motor imagery
MMPI-2	Minnesota Multiphasic Personality Inventory-2
MOP	mu opioid
MPQ	McGill Pain Questionnaire
MR	modified release
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant Staphylococcus aureus
MS	multiple sclerosis
MSE	mental state exam
MSK	musculoskeletal
MSU	monosodium urate
MTP	metatarsophalangeal
MTrP	myofascial trigger point
Na^+	sodium
NAPQI	N-acetyl-p-benzo-quinone imine
NASS	National Ankylosing Spondylitis Society
NCS	nerve conduction study
NGF	nerve growth factor
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIPS	Neonatal/Infant Pain Scale
NIRS	near infra-red spectroscopy
NK1	neurokinin-1
NK2	neurokinin-2
NLP	neurolinguistic programming
NMDA	N-methyl-D-aspartic acid
NMJ	neuromuscular junction
NNH	number needed to harm
NNT	number needed to treat
NO	nitric oxide
N_2O	nitrous oxide
NOP	nociceptin opioid peptide
NPQ	Neuropathic Pain Questionnaire
NPS	Neuropathic Pain Score
NPV	negative predictive value
nr-ax SpA	non-radiographic axial spondyloarthritis
NRS	Numeric Rating Scale
NRTI	nucleoside reverse transcriptase inhibitor

NSAID non-steroidal anti-inflammatory drug
NSC non-selective cation channel
nsNSAID non-selective NSAID
NT neurotransmitter
OA osteoarthritis
OCD obsessive–compulsive disorder
OCF osteoporotic compression fracture
ODI Oswestry Disability Index
OH hydroxyl group
OIH opioid-induced hyperalgesia
OLP open-label placebo
OMEDD oral morphine equivalent daily dose
ONS occipital nerve stimulation
OR odds ratio
ORT Opioid Risk Tool
OST opioid substitution therapy
OT occupational therapy
OXC oxcarbazepine
PA posteroanterior
$PaCO_2$ Partial pressure of carbon dioxide
PACSLAC Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PACU Post-anaesthesia care unit
PAG periaqueductal grey area
PAINAD Pain Assessment in Advanced Dementia (scale)
PaO_2 Partial pressure of oxygen
PBCL Procedure Behaviour Checklist
PCA patient-controlled analgesia
PCR polymerase chain reaction
PCS Pain Catastrophizing Scale
PCT proximal convoluted tubule
PD personality disorder
PDUQ Prescription Drug Use Questionnaire
PE pulmonary embolus
PEG polyethylene glycol
PENS percutaneous electrical nerve stimulation
PET positron emission tomography
PG prostaglandin
PGI2 prostacyclin
PHN post-herpetic neuralgia
PHQ Patient Health Questionnaire
PIP psychologically informed physiotherapist
PIPP Premature Infant Pain Profile
PMMA polymethylmethacrylate
PMP pain management programme
PNFS peripheral nerve field stimulation
PNS peripheral nerve stimulation
PO per oral
POMS Profile of Mood States
PPV positive predictive value
PRF pulsed radiofrequency
PRN as needed (Latin: pro re nata)
PROSPECT PROcedure-SPECific post-operative pain managemenT
PRP platelet-rich plasma
PSEQ Pain Self-Efficacy Questionnaire
Psi pound per square inch
PSIS posterior superior iliac spine
PTNS percutaneous Posterior Tibial Nerve Stimulation
PTSD post-traumatic stress disorder
QLB quadratus lumborum block
QLM quadratus lumborum muscle
QoL quality of life
QST quantitative sensory testing
RA rheumatoid arthritis; rectus abdominis
rACC rostral anterior cingulate cortex
RAD radiation absorbed dose
RBC red blood cell
RCT randomized controlled trial
RDA recommended daily allowance
Relim rate of drug elimination
REM radiation equivalent in man
RF radiofrequency
RFS Risk Fracture Score
RMP resting membrane potential
RNA ribonucleic acid
RNP ribonucleoprotein
ROM range of movement
RR respiratory rate; risk reduction; relative risk
RS respiratory system
rTMS repetitive transcranial magnetic stimulation
RVM rostroventral medulla
SA sinoatrial
SC subcutaneous
SCI spinal cord injury
SCJ sternoclavicular joint
SCL superior costotransverse ligament

SCS spinal cord stimulation
SD standard deviation
SDS Severity of Dependence Scale
S/E side effect
SEM standard error of the mean
SENS subcutaneous peripheral nerve stimulation
SEP sensory evoked potential
SG substantia gelatinosa
SIADH syndrome of inappropriate antidiuretic hormone
SIGN Scottish Intercollegiate Guidelines Network
SIJ sacroiliac joint
SIS Spine Intervention Society
SISAP Screening Instrument for Substance Abuse Potential
SJS Stevens–Johnson syndrome
SLE systemic lupus erythematosus
SNAP sensory nerve action potential
SNP single nucleotide polymorphism
SNRI serotonin and noradrenaline reuptake inhibitor
SNS sympathetic nervous system
SOAPP Screener and Opioid Assessment for Patients with Pain
SP substance P
SPECT single-photon emission computed tomography
SPG sphenopalatine ganglion
SpO_2 oxygen saturation
SSCS Stress Symptoms Checklist
SSD somatic symptom disorder
SSN suprascapular nerve
SSNRI selective serotonin–noradrenaline reuptake inhibitor
SSRI selective serotonin reuptake inhibitor
STIR short tau inversion recovery
SUA serum uric acid
SUNA short-lasting unilateral neuralgiform headaches with cranial autonomic symptoms
SUNCT short-lasting unilateral neuralgiform headaches with conjunctival tearing
$t^{1/2}$ half-life
TA transverse abdominis
TAC trigeminal autonomic cephalgia
TAP transverse abdominis plane
TB tuberculosis
TC therapeutic community
TCA tricyclic antidepressant
TCM traditional Chinese medicine
TEN toxic epidermal necrolysis
TENS transcutaneous electrical nerve stimulation
TFESI transforaminal epidural steroid injection
TFT thyroid function test
THC delta-9-tetrahydrocannabinol
THCV tetrahydrocannabivarin
TLR Toll-like receptor
TLR4 Toll-like receptor
TMD temporomandibular disorder
TN trigeminal neuralgia; true negative
TNF tumour necrosis factor
TON third occipital nerve
TP transverse process; true positive
TPI trigger point injection
TRP transient receptor potential
TRPV transient receptor potential vanilloid
TSH thyroid-stimulating hormone
TV tidal volume
TXA2 thromboxane
UGT uridine 5′-diphospho-glucurosyltransferase
UMN upper motor neuron
US ultrasound
USS ultrasound scan
UV ultraviolet
VAS Visual Analogue Scale
Vd volume of distribution
VGAT vesicular GABA transporter
VH ventral horn
VMAT vesicular monoamine transporter
VNS vagus nerve stimulation
VRS Verbal Rating Scale
VZV varicella zoster virus
WAD whiplash-associated disorder
WC white commissure
WDR wide dynamic range
WHO World Health Organization
w/v weight by volume

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SECTION 1

OVERVIEW OF PAIN

CHAPTER 1

Types of Pain and Pain Assessment

Sabina Bachtold, Enrique Collantes, Praveen Ganty, Yehia Kamel, Gustav Jirikowski, Deepak Ravindran, Jan Rudiger, Alifia Tameem, and John Tanner

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1.1 Acute/chronic pain and IASP classi cation of chronic pain for ICD-11

De nition

P

'*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*' [1]

P

'*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*' [2]

P

'Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors'[3]

P

'Pain caused by a lesion or disease of the somatosensory nervous system' [3]

1. Reproduced with permission from Raja, S., N., *etal.(2020)*. The revised International Association for the Study of Pain de nition of pain: concepts, challenges, and compromises, *Pain*. 161(9): 1976–1982. doi: 10.1097/j.pain.0000000000001939.
2. Reproduced with permission from The need of a taxonomy. *Pain*, 6(3). 247–252, 1979. DOI: 10.1016/0304-3959(79)90046-0
3. Reproduced from Kosek E, et al. Do we need a third mechanistic descriptor for chronic pain states?, Pain, 157(7): 1382–1386, copyright 2016, International Association for the Study of Pain.

Table 1.1.1 Di erence between acute and chronic pain

Acute pain	Chronic pain
At the same time with an acute illness/injury	Persists beyond the expected time of healing (3 months)
Warning system to alert the body to a problem	Serves no physiological purpose
Predominantly nociceptive	Frequently neuropathic in nature
Usually resolves with complete tissue healing	Persistent
Inadequate treatment can lead to chronic pain states	Negative impact on quality of life. High costs to society

P

'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' [3]

The di erence between acute and chronic pain

(See Table 1.1.1.)

Transition from acute to chronic pain

The mechanisms that might underlie the transition are not yet fully understood but may be minimized by early recognition of risk factors (see Table 1.1.2) and early biopsychosocial pain management

P

Continuous and prolonged in ammatory reaction releases pro-nociceptive factors, such as cytokines, prostaglandins (PGs), substance P (SP), tumour necrosis factor (TNF) alpha, and interleukins (ILs), resulting in decreased activation thresholds and spontaneous discharge

Peripheral sensitization occurs, causing allodynia and hyperalgesia within an area of in amed skin

Table 1.1.2 Risk factors for transition from acute to chronic pain

Pre-existing	At the time of injury/surgery	Post-injury/surgery
Pre-existing pain in the area High opioid use Female—higher scores Age (children < elderly < young) Raised BMI Genetic polymorphism Radiation therapy Psychological vulnerability Psychosocial issues Yellow ags Blue ags Black ags Other chronic conditions	Type of surgery (amputation, breast surgery, thoracotomy, hernia repair, coronary artery bypass, Caesarean section) Operations >3 hours Surgical technique Repeat surgery	Severe post-operative pain Poorly treated acute pain Catastrophizing

β

Intense nociceptive activation leads to changes in the dorsal root ganglion (DRG) and dorsal horn (DH) neurons, increasing sodium (Na^+) and transient receptor potential vanilloid (TRPV) 1 receptor and activation of the N-methyl-D-aspartic acid (NMDA) receptor

There is a phenotypic switch, cross-sprouting with receptive fields on the DH being widened

Central sensitization arises in undamaged tissue away from the site of injury, with secondary allodynia or hyperalgesia. The application of noxious heat and capsaicin has been shown to produce secondary hyperalgesia and reversible changes in the brainstem of human volunteers. This reversible form of central sensitization has been termed 'wind-up'

Transcription-dependent central sensitization is more permanent and occurs if the stimuli triggering central sensitization continue causing new synaptic connections to be made and there may even be death of certain cells. This more permanent form of sensitization may even result in structural changes in the brain that are visible on magnetic resonance imaging (MRI) scanning

B

Functional MRI (fMRI) and positron emission tomography (PET) scans confirmed changes that occur in the pain matrix (thalamus, mid/anterior insula, anterior cingulate and prefrontal cortex, periaqueductal grey area (PAG) and rostroventral medulla (RVM), reticular formation, and amygdala) with increased functional connectivity between the medial prefrontal cortex and nucleus accumbens (the brain's emotion learning circuits) being highly predictive of chronicity

Strong correlation between mental health of the patient and chronic pain leading to maladaptive coping habits

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1.2 History taking in pain medicine

Principles

A thorough, comprehensive history helps in establishing a good relationship with the patient and to formulate a comprehensive multimodal treatment plan

Follow the principles of VEMA—Validate their symptoms, Educate the patient, Motivate them, and provide them the tools for Activation

Screen all patients for pain and perform a comprehensive pain assessment

Common elements of a thorough, semi-structured interview include:

- Experience of pain and related symptoms and factors influencing it
- Treatments received and ongoing

Current litigation status, if any
Coping abilities
Educational/vocational/work/employment status
Any relevant psychosocial history, including adversity in childhood, if relevant
Alcohol and any substance misuse
Ongoing psychological issues, if any
Concerns and explanations for pain
Treatment goals

Set the stage

Reassure patients that you take their pain seriously, and understand its impact and the need for treatment

Maintain a respectful and professional attitude

It is important to believe the patient's reports of pain and distress, particularly in the case of patients with chronic non-cancer pain (CNCP) who may have had di cult encounters with previous health care professionals

Even if psychological issues or addiction are present, respectful validation of the patient's su ering is invaluable to assessment and will lead to more e ective treatment planning

Pain is a multi-dimensional phenomenon that can produce strong emotional reactions that impact on function, quality of life (QoL), emotional state, social and job status, and general well-being

Pain assessment should also be multi-dimensional: evaluate these various elements during the interview and examination, and include them in the diagnostic formulation

A thorough history and physical examination are essential for the medical and pain diagnosis and treatment planning

Careful attention to the patient's reported symptoms will help direct the physical examination and narrow the pain di erential diagnosis

Perform complete neurological and musculoskeletal (MSK) examinations

Additional testing, such as imaging and laboratory studies or electrophysiological testing (electromyography (EMG)/nerve conduction studies), may be ordered as needed, based on the results of the history and examinations

The RAT model

(See Table 1.2.1.)

Table 1.2.1 The RAT model

Recognize pain	Does the patient have pain? Do other people (carers/family) know that the patient is in pain?
Assess pain	Measure the severity What is the pain score at rest? With movement? How is the pain a ecting the patient? What scales would you use? Make a diagnosis Acute or chronic Cancer or non-cancer Nociceptive/neuropathic or mixed or nociplastic Are there other factors? Psychological factors Physical factors (other illnesses)
Treat	Non-drug and drug strategies

Table 1.2.2 Simple steps to make a provisional pain diagnosis

What is the duration of pain?	Acute Chronic Acute-on-chronic
What is the main cause of pain?	Cancer Non-cancer
What is the suspected mechanism?	Nociceptive. Neuropathic Mixed (nociceptive and neuropathic) Nociplastic

The Faculty of Pain Medicine (UK) advises all health care professionals to consider using the RAT model as a simple framework for patients with pain:

R for 'Recognize pain'

A for 'Assessment of pain'

T for 'Treat the pain using non-drug and drug strategies'

Another simple way to assess pain is shown in Table 1.2.2

Pain scales

Pain is a subjective experience with a di erent meaning to each person

Changes in pain intensity are valuable when measured for single individuals (e.g. before and after a treatment)

Pain intensity measures should not be used to compare pain between di erent individuals. One person's 4/10 might be another's 10/10

A numeric pain rating scale for most clinical settings. The most common one is the 11-point Likert scale where 0 = no pain and 10 = worst pain imaginable

For children, consider using the 0–5 Wong-Baker Faces scale (see Table 1.2.3)

Non-verbal patients (e.g. those in coma or with dementia or other cognitive impairments) must be assessed for pain by the Abbey Pain scale and by other observational means (e.g. body language, movement, autonomic arousal, and non-verbal pain behaviour)

The pain history interview

A number of mnemonic-based, structured history taking approaches are available such as SOCRATES (see 1.13 Mnemonics for referrals p. 42) or PAIN FRAME

The mnemonic 'QISS TAPED' is a comprehensive tool to help ensure all information is sought (see Table 1.2.4)

Table 1.2.3 Types of pain assessment tools

Uni-dimensional tools	Verbal Rating Scale Numerical Rating Scale Visual Analogue Scale Faces scale (Wong-Baker scale)
Multi-dimensional tools	McGill Pain Questionnaire Brief Pain Inventory West Haven-Yale Multi-dimensional Pain Inventory (WHYMPI) Medical Outcome Study 36-item Short-form Health Survey (SF-36)
Screening tools for neuropathic pain	Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Neuropathic Pain Questionnaire (NPQ) DN4 PainDETECT

Table 1.2.4 Pain assessment mnemonic (QISS TAPED)

Q	Quality	What were your first symptoms? What words would you use to describe the pain (aching, sharp, burning, squeezing, dull, icy, etc.)?
I	Impact	How does the pain affect you? What does the pain prevent you from doing? (Depression screen) Do you feel sad or blue? Do you cry often? Is there loss of interest in life? Decreased or increased appetite? (Anxiety screen) Do you feel stressed or nervous? Have you been particularly anxious about anything? Do you startle easily?
S	Site	Show me where you feel the pain. Can you put your finger/hand on it? Or show me on a body map? Does the pain move/radiate anywhere? Has the location changed over time?
S	Severity	On a 0–10 scale, with 0 = no pain and 10 = the worst pain imaginable, how much pain are you in right now? What is the least pain you have had in the past (24 hours, 1 week, 1 month)? What is the worst pain you have had in the past (24 hours, 1 week, 1 month)? How often are you in severe pain (hours in a day, days in a week you have pain)? Consider using Brief Pain Inventory if possible
T	Temporal characteristics	When did the pain start? Was it sudden? Gradual? Was there a clear triggering event? Is the pain constant or intermittent? Does it come spontaneously or is it provoked? Is there a predictable pattern? (e.g. always worst in the morning or in the evening? Does it suddenly wake you up?)
A	Aggravating and alleviating factors	What makes the pain better? What makes the pain worse? When do you get the best relief? How much relief do you get? How long does it last?
P	Past response, preferences	How have you managed your pain in the past? (Ask about both drug and non-drug methods) What helped? What did not help? (Be specific about drug trials—how much and for how long?) What medications have you tried? Was the dose increased until you had pain relief or side effects? How long did you take the drug? Are there any pain medicines that have caused you an allergic or other bad reaction? How do you feel about taking medications? Have you tried physical or occupational therapy? What was done? Was it helpful? Have you tried spinal or other injections for pain treatment? What was done? Was it helpful?
E	Expectations, goals, meaning	What do you think is causing the pain? How may we help you? What do you think we should do to treat your pain? What do you hope the treatment will accomplish? What do you want to do that the pain keeps you from doing? What are you most afraid of? (Uncover specific fears, such as fear of cancer, which should be acknowledged and addressed)
D	Diagnostics and physical examination	Examine and inspect the site Perform a systems assessment and examination as indicated Review imaging, laboratory, and/or other test results as indicated

A pain history should include location, quality, intensity, temporal characteristics, aggravating and alleviating factors, impact of pain on function and QoL, past treatment and response, and patient expectations and goals. Table 1.2.4 summarizes the general categories that should be addressed during a pain assessment, along with examples of questions that may be useful during the interview

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1.3 Examination in the pain clinic

Introduction

Pain clinic examination needs to be as broad and deep as the history taking aspect

Examination is a good opportunity to re-evaluate the entire clinical presentation

Do not assume that your colleague's referral and examination are correct

One commonly hears from the patient, after a thorough clinical examination, that 'this is the first time someone has actually taken the trouble to examine me in detail' despite having seen several other clinicians

Patients appreciate attention to detail, and trust and confidence will be established early

The history is 80–90% of the diagnosis, but the examination needs to be thorough and detailed to support or refute the diagnostic label (already supplied in most cases) and to provide further specific information regarding the degree of physical impairment, disability, and pain characteristics

The examination can be divided into *general health and system examination*, and *regional examination*

General health and system examination

Clinicians are generally good at recognizing unwellness through pallor, breathlessness, flushed skin, unusual discoloration, grey or sallow complexions, and rapid pulse

The opioid-dependent patient may have a faint layer of sweat, glassy eyes, tremor, and flat affect

Unexplained features need to be evaluated carefully from a medical point of view, looking at the skin, hands, and nails, with a brief assessment of the cardiovascular system (CVS), abdominal palpation, and other systems, and reviewing medication

Unexplained rash, itching, or excoriation need to be identi ed

Signs of self-harm, whether recent or old, indicate previous mental health problems

Assessment of posture, gait, and mobility is essential (do not commence the examination on the couch)

MSK issues: osteoarthritic knees or hips, e usions, muscle wasting, deformities

Screen all widespread pain patients for hypermobility according to the Brighton criteria

Obesity and metabolic issues complicate many aspects of management

General demeanour: a ect, responsiveness, ability to communicate (assessment via an interpreter is an unfortunate compromise)

Pain patients may simply have a nociceptive source such as a speci c nerve entrapment

Peripheral and central sensitization features of neuropathic pain: hyperalgesia or allodynia, cutaneous hyperaesthesia, and possible sensory or motor impairment

Patients may have a host of psychosocial issues: depression, anxiety, and unhelpful beliefs about the nature of their pain which a ect their communication and expression of the pain (identi ed in their *painbehaviour*)

Fear of pain and pain avoidance are common (secondary gain factors may drive this)

Subconscious post-traumatic stress can cause fear and anxiety about their pain condition

Complex regional pain syndrome (CRPS) in a limb extremity: patients show disa ectation or dissociation from the painful part (lack of voluntary movement is common)

Faulty movement patterns as a result of inhibition, weakness, or pain avoidance

Cooperation and consent for a thorough examination of all these aspects must be sought with a statement like 'I would now like to examine you very carefully …'

Undressing must be su cient to inspect, assess range of motion, and palpate adequately

Before any examination, ask the patient to indicate where the pain is or, if absent, at what point the movement provokes it and where

Depending on the presentation, a neurological examination of the cranial nerves (CNs) and/or peripheral nervous system is needed. Examination of CNs is covered in 16.1 Cranial nerves, p. 299. Upper and lower limb neurological examination includes an assessment of muscle tone, power, re exes, coordination and sensation (temperature, pinprick, proprioception, light touch, deep touch, brush, sensory mapping) which is covered subsequently in this chapter

Regional examination



Patient standing or sitting (examiner behind)

Assess posture (forward head?)

Muscle wasting or hypertrophy—trapezii muscles

Active range of motion assesses willingness

Passive range of motion (to assess end-range feel)

Foraminal closing test for radicular symptoms (Spurling's test combining extension, ipsilateral rotation, and side-bending sustained, but without axial compression)

Shoulder: active range of elevation and controlled descent

Examine upper limbs for referred pain or if neurological de cit for radicular symptoms

Patient supine

Palpate suboccipital muscles for tender points (localized pain on one side increased by passive exion may indicate greater occipital nerve entrapment) and other paraspinal muscles (e.g. scalenus muscles)



Figure 1.3.1 Palpation points on cervical articular column

Passive range of nutation at atlanto-occipital joint (usually restricted with cervical extensor muscle shortening or tension)

Passive rotation at atlanto-axial joints (painful restriction of rotation in one direction indicates C1–2 arthropathy)

Segmental side gliding for tenderness or localized restriction (ngertips placed at 4 and 8 o'clock over the articular column) identi es dysfunctional level for treatment (see Figs. 1.3.1 and 1.3.2)

Patient prone

Palpate the medial scapular muscles and trapezii for tender/trigger points and upper thoracic spine segments

Note: A subroute if thoracic outlet syndrome is suspected: Roos test (hands up), Lindgren's rst rib assessment, palpate the supraclavicular fossa and scalenus muscles, neurological assessment of the upper limb

Benign pain is common, but referred pain or metastases from malignancy or viscera are not uncommon (in the elderly, compression fractures are often missed)

Patient stripped to waist (with bra). Note deformities and scoliosis, angular kyphosis on *standing*

Patient sitting

Observe chest movement with breathing and abnormal pattern (breath holding or hyperventilation)

Measure chest expansion in suspected ankylosing spondylitis

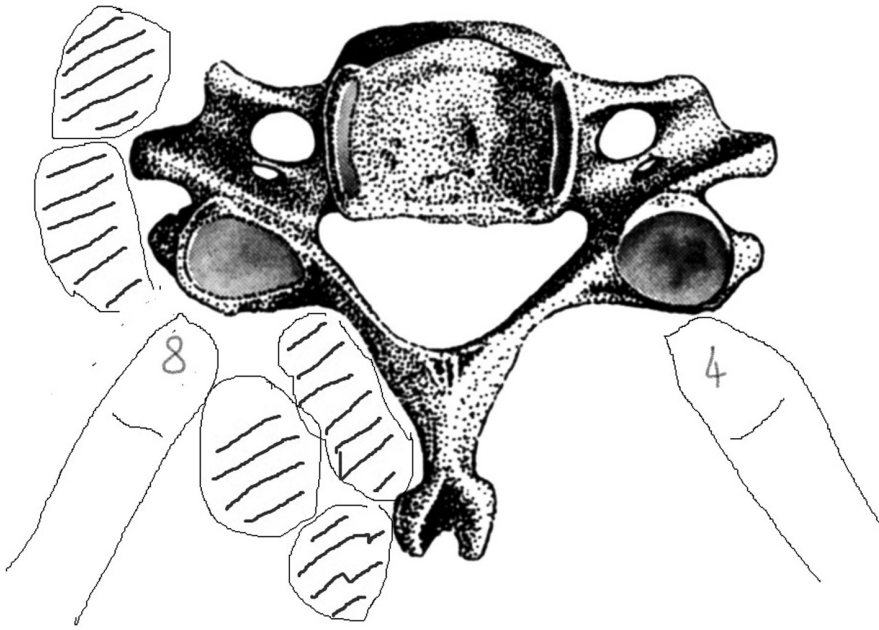


Figure 1.3.2 Fingertips placed at 4 and 8 o'clock over the articular column

Observe active rotation, side-bending, flexion, and extension in sitting, inspecting from behind (symmetric limitation suggests spondyloarthropathy, whereas asymmetric limitation suggests dysfunction)

Localized percussion of segments for exquisite pain

Patient prone

Palpate spinous processes with posterior–anterior and lateral pressures to identify segmental dysfunction

Repeat localized percussion if indicated

Palpate paravertebral gutters for muscle tenderness, trigger points, and deeper facet joint tenderness. Palpate costo-transverse joints and rib movements and intercostal muscles with inspiration and expiration

Patient supine

Palpate costo-chondral junctions for swelling or tenderness

Patient standing

Assess stance from behind—is the pelvis level and the spine straight?

Is there an antalgic position, e.g. deviation to one side?

Inspect for scoliosis in full flexion and extension (i.e. rib hump)

Active side-bending (rotation not necessary unless combined with side-bending for possible facetal pain and stress fracture)

Extension with side-bending may elicit radicular pain in foraminal stenosis

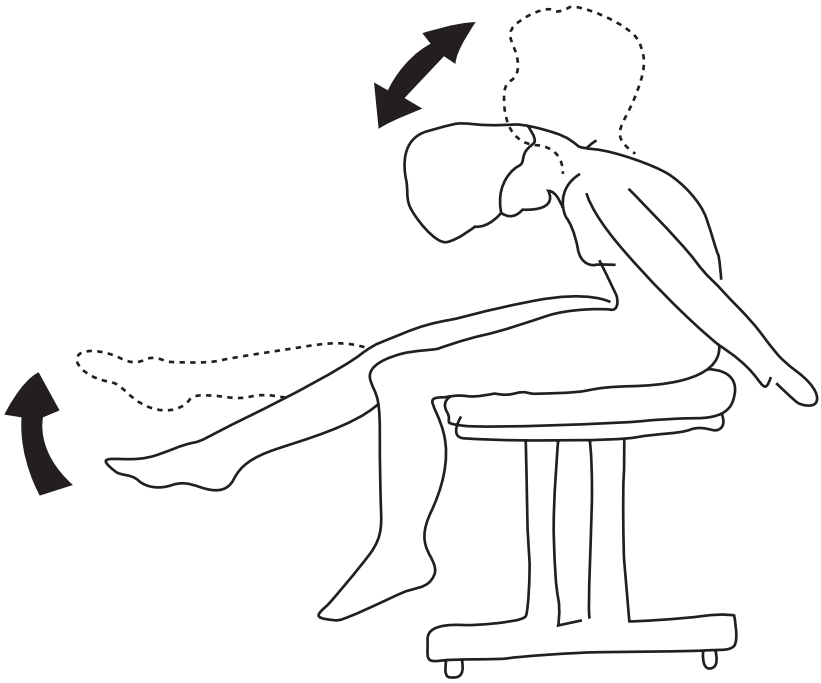


Figure 1.3.3 The slump test identi es dural in ammation usually related to disc herniation

Forward exion—is the spine exing (consider modi ed Schober's test) or are the hips?
Consider uency and cadence—catch pains and deviatory arcs of movement, as well as ngertip-to- oor distance
Modi ed Schober's test: while the patient is in full forward exion, place your outstretched thumb and index in the midline to span the patient's lumbo-sacral area, with your thumb at the level of the posterior superior iliac spines and your index as high as you can reach on the spine. The span between these digits will be about 15 cm. Ask the patient to extend up to a neutral erect position. The span between your thumb and index should decrease by around 5 cm. Less than 3 cm will indicate signi cantly decreased lumbar spinal exion
Ask to squat: competence of lower limb joints and muscles
Trendelenburg's test for hip dysfunction
Ask the patient to raise each heel o the ground as far as possible (supporting them with the hands if necessary) to test S1 myotome
Ask them to rock back on the heels, looking for signs of a partial foot drop

Patient sitting

Slump test for dural tension (more sensitive than straight leg raise test) (see Fig. 1.3.3)
Are iliac crests level? (consider leg length di erence or scoliosis)

Patient supine

Log roll each leg rmly, observing rebound if normal laxity, and whether pain is provoked in the hip at either extreme of internal or external rotation
Measure leg length (anterior superior iliac spines (ASIS) to medial malleoli)

Passive knee and hip range of motion testing before straight leg raise test

Sacroiliac pain provocation tests:

Anterior compression and distraction

Axial thigh thrust or P4 test (ex one hip to 90° and align the knee vertically over the sacroiliac joint (SIJ); apply rm impulse pressure through the axis of the femur to provoke pain in the posterior SIJ region. Compare both sides. Caution: lumbar pain may also be provoked by this test if lordosis is not supported (use the patient's hand). The same false positive may occur with anterior compression or distraction tests.

Gaenslen's test (move the patient to one side of the couch and bring one hip and knee into full exion; then drop the other hip and knee into full extension o the side of the couch to provoke pain in either joint. Repeat on other side)

Faber's test (**F**lexion—**Ab**duction—**E**xternal **R**otation) of one hip—apply overpressure to the ipsilateral knee (pain must be provoked in the posterior SIJ region. Test is not valid with any associated hip or adductor/symphysis problem)

Perform sensory, re ex, and motor tests for lumbar radiculopathy, including plantar responses for upper motor neuron (UMN) lesion

Patient prone

Femoral nerve stretch test

Post-sacral spring test (for SIJ)

Buttock clench test for S1 myotome

Spring in a postero-anterior direction the lumbar spinous processes, rst gently, then deeply for segmental pain

Palpate the SIJ sulcus and paravertebral muscles and facetal areas for tenderness

Patient side-lying or in decubitus position

Lateral compression (for SIJ)

Palpate the trochanteric area for tenderness over the trochanter or gluteus medius/minimus tendons and piriformis and hip external rotators

Palpation over the sciatic foramen is unreliable for piriformis syndrome diagnosis. Test shortening of external hip rotators in supine position by laterally rotating the hip; maintain while slowly bringing towards greater exion. Pain and reproduction of symptoms occur earlier than on the normal side

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1.4 Dermatomes and myotomes

De nitions

Areas of skin that receive sensory innervation from a speci c cranial or spinal nerve

Sensory neurons are located either in the DRGs or in the trigeminal ganglia (ganglion Gasseri or nucleus spinalis V)

- Each of these nerves relays sensations (including pain) from a particular skin region to the dorsal horn of the spinal cord or to the brain

Myotomes

- Groups of skeletal muscles that receive motor innervation from the ventral root of a single cranial or spinal nerve
- Motor neurons are located in the motor nuclei of the brainstem or in the ventral horn of the spinal cord

Anatomy

Dermatomes

(See Fig. 1.4.1.)

Trigeminal nerve:

V1: forehead, eye

V2: upper face, nose

V3: lower face, chin

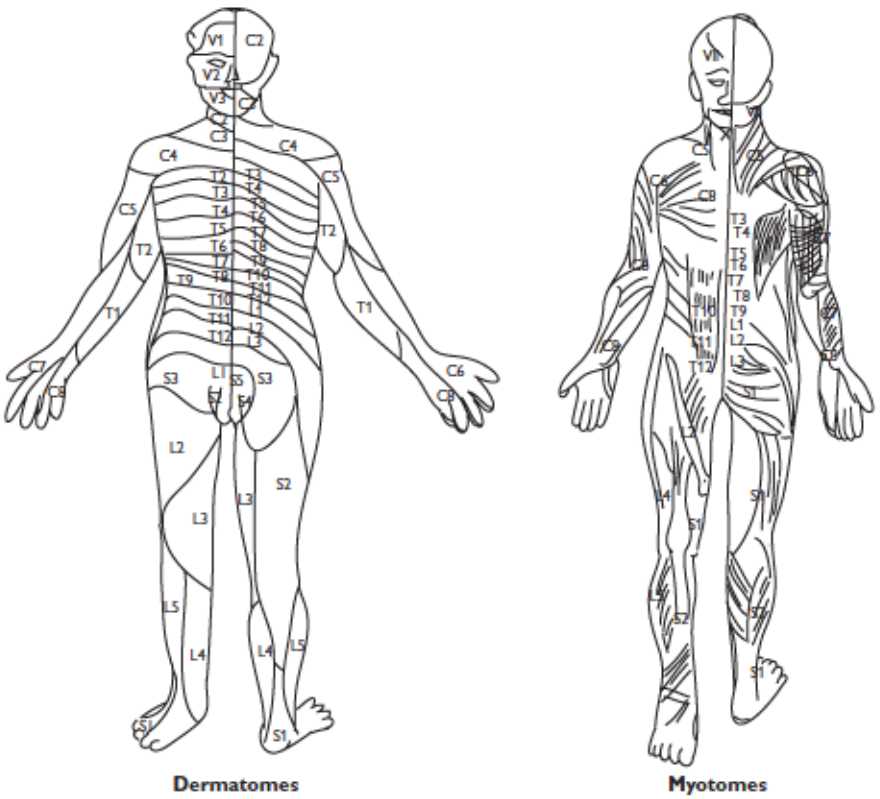


Figure 1.4.1 Human dermatomes and myotomes, and innervation of bones and other skeletal tissues (sclerotomes)

Cervical nerves:
- C2: base of the skull
- C3: supraclavicular and mid-clavicular line
- C4: acromion
- C5: cubital fossa and elbow
- C6, C7, C8: upper arm, forearm, and hands

Thoracic nerves:
- T1: medial aspect of the forearms
- T2: axilla and medial aspect of upper arms
- T3–T8: corresponding intercostal spaces
- T9: area between xiphoid process and umbilicus
- T10: umbilical region
- T11: lower abdomen
- T12: inguinal region

Lumbar nerves:
- L1: inguinal region and upper anterior thigh above L2
- L2: antero-medial thigh
- L3: antero-medial aspect of the knee
- L4: medial aspect of the lower leg and medial ankle
- L5: lateral aspect of the leg, dorsal aspect of the foot and heel

Sacral segments:
- S1: postero-lateral leg, lateral aspect of the foot and sole of the foot ± heel
- S2: postero-medial leg, popliteal fossa
- S3: ischium and infra-gluteal fold
- S4–S5: perianal area

M

(See Fig. 1.4.2.)

Trigeminal nerve: V1: jaw muscles, tensor tympani

Facial nerve: mimics muscles, M. stapedius

Vagus nerve: larynx

Cervical segments:
- C1/2/3: neck exion/extension
- C4: shoulder elevation, diaphragm (phrenic nerve)
- C5: shoulder abduction (axillary nerve)
- C6/7/8: shoulder adduction
- C5: elbow exion (musculocutaneous nerve)
- C7: elbow extension (radial nerve)
- C6/7: wrist exion and extension
- C7: nger extension (radial nerve)
- C8: nger exion (median nerve)

Thoracic segments:
- T1: nger abduction (ulnar nerve), thumb abduction (median nerve)
- T1–T12: intercostal muscles, abdominal muscles, paravertebral back muscles

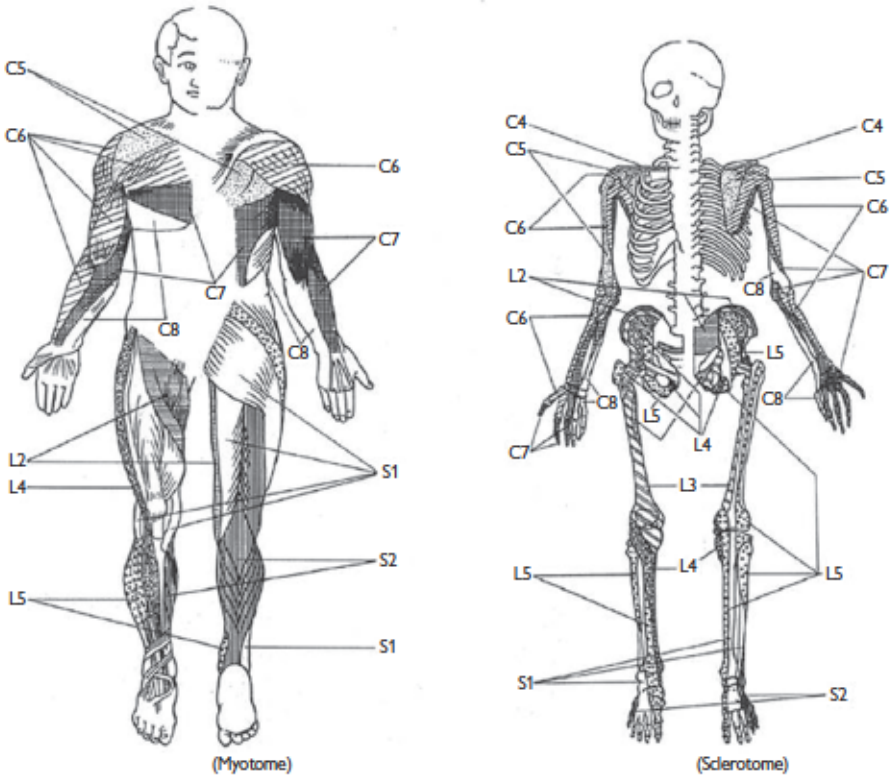


Figure 1.4.2 Myotomes, innervation of bones and other skeletal tissues (sclerotomes)

Lumbar segments:

L2: hip flexion (femoral nerve); L5: hip extension (inferior gluteal nerve)

L3/4: knee extension (femoral nerve)

L4: ankle dorsiflexion (deep peroneal nerve)

L5: big toe dorsiflexion (deep peroneal nerve)

Sacral segments:

S1: ankle plantarflexion, foot eversion, hip extension

S2: knee flexion

S3–S4: perineal region and anal sphincter

Clinical relevance

- Dermatome testing assesses distribution of pain symptoms and reduced sensation to determine the level of a spinal nerve lesion (e.g. after disc prolapse). However, there can be overlapping supply of spinal nerves to dermatomes
- Visceral sensations can map to specific dermatomes. Some sensations are felt locally, whereas others are perceived over areas that are more distant from the involved organ ('referred pain'). Pain in the left shoulder can indicate angina pectoris. These dermatomes are referred to as 'head zones'

Viral infections of ganglia (e.g. varicella zoster virus (VZV)) can cause either pain or rash, or both, in a pattern de ned by a dermatome or part of it (zosteriform pattern)

Testing of myotomes is more reliable than dermatomal testing in determining the level of a spinal nerve root lesion or irritation. Isometric resisted muscle strength is tested. Assessment of muscle weakness in a particular region could indicate a lesion of the spinal cord, nerve root, or an intervertebral disc herniation/prolapse

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1.5 Flags in pain medicine

Di erent colour ags are used to identify a serious pathology or an underlying concern, and to help triaging patients within the pain service and to other health care professionals and to consider further investigations

Many of these presentations can be transferred to other pain conditions

Red ags (organic pathology)

History, signs, and symptoms that could denote a serious medical condition with an underlying pathology such as:

- Age of onset <20 years or >55 years
- History of serious pathology (e.g. carcinoma)
- Ill health (acutely unwell) or presence of other medical illness or infection (e.g. human immunode ciency virus (HIV), spinal tuberculosis (TB), ischaemia)
- Thoracic pain
- Severe unremitting night pain, night fever
- Progressive neurological de cit (weakness ± sensory de cit)
- Disturbed gait, saddle anaesthesia
- Vertebral fracture or deformity (e.g. traumatic or osteoporotic)
- Unexplained weight loss (e.g. >10% body weight in last 3–6 months)
- Bladder or bowel dysfunction (e.g. in cauda equina)
- Immunosuppression
- History of corticosteroid use
- History of intravenous (IV) drug use

Although there has been recent controversy about its utility, red ags still remain integral to many guidelines for triaging patients

The recommendation is to pursue further investigations and refer to a specialist

Yellow flags (psychological and behavioural)

These refer to psychosocial and environmental factors that could interfere with assessment and management plans, in addition to long-term pain and associated disability

They tend to be in the domains of patients' beliefs, judgements, appraisals, emotional responses, pain behaviour, and coping strategies:

- A negative belief that their pain is damaging or potentially severely disabling
- A belief in the lack of benefit from treatment
- Fear avoidance behaviour
- Lack of acceptance
- Poor coping, reduced self-efficacy
- Maladaptive behaviour/cognition
- Diminished activity levels/activity pattern that aggravate pain
- A reliance on passive treatment modalities (analgesia, interventions, cold packs, hot packs)
- A tendency to depression, worries, fears, and anxiety
- Social withdrawal
- Social or financial problems
- Increased drug use, reliance on aids (smoking)
- Secondary gain (e.g. overprotective family)
- Litigation, compensation

Managed by strategies to tackle the maladaptive beliefs through education and psychological approach

Orange flags (referral to mental health team if not optimized)

Psychiatric illness
Major personality disorder
Post-traumatic stress syndrome
Psychosis
Addiction
Increased levels of distress
Suicidal ideations

Blue flags (work perception)

An individual's perception of work (if accurate or not) about the relationship between the employment or the nature of the work performed and the state of health, with a belief that it may negatively impact their pain

Patients could also encompass a belief that their superiors and colleagues are unsupportive

Unemployment, poor job satisfaction

Fear of (re-)injury at work, stress at work

Black flags (work conditions)

Actual contextual work place or insurance obstacles that could delay a return to work and perpetuate the condition

May include legislation that restricts the options of those attempting return to work

It may also include objective work demands or conditions such as heavy, physically demanding duties that have not been modi ed

Unsociable hours

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1.6 Mental state exam

Introduction

Mental state exam (MSE) is essential for the biopsychosocial assessment of pain patients, especially in patients that also have mental health conditions

Involves a systematic assessment of the appearance, behaviour, speech, mood, a ect, mental functioning, and overall demeanour of a person

Provides a snapshot of the psychological function of a person which helps to understand the factors that in uence experience, behaviours, distress, and su ering of patients

MSE enables the detection of conditions which need to be treated simultaneously with pain to achieve a good outcome. These conditions can include mood disorders, panic disorders, post-traumatic stress disorder (PTSD), disorders of cognitive impairment (e.g. stroke, dementia, head injury), personality disorders (PDs), substance use disorders, and other psychiatric conditions

Every time clinicians interact with patients, they intuitively perform many parts of the MSE

Domains of a mental state exam

A

Can provide clues of patients' lifestyle, well-being, health, nutrition, and functioning on a daily basis

Components normally evaluated include body posture, body built, nutritional features, clothing, grooming, skin (colour, tattoos, marks, scratches), ngers/hands, distinctive features, ethnicity, cosmetics, jewellery, evidence of physical deconditioning, malnourishment, and sequelae of having chronic diseases

B

Verbal and non-verbal behaviours provide a picture of the emotional state, attitude, appropriateness, activity levels, and response of the patient to the clinician (e.g. cooperative, willing to disclose information)

The following are evaluated: body language (calm, agitated, restless, withdrawn), rapport, facial expressions, mannerism, eye contact, interactive style, movements (repetitive, slowed, involuntary, tremors), and hallucinatory behaviours

[illegible]

A ect describes the immediate expressions which describe a patient's current emotional state. A ect can be described in terms of its appropriateness (inappropriate or appropriate), range (blunted, at, restricted, expansive, labile), and stability (non-stable or stable). A ect is sometimes described as 'how the patient's emotional state is perceived by the clinician conducting the consultation'

Mood describes a patient's emotional state over days/weeks/months. A patient's mood can be depressed, neutral, irritable, anxious, angry, or apprehensive. Mood can be stable or labile. Mood can also be described as 'how the patient describes their emotional state over a period of time of days/weeks'

[illegible]

Certain speech patterns can be found in some conditions such as anxiety, depression, schizophrenia, and organic diseases

The aspects of speech normally evaluated include the rate, amplitude, modulation, and ease of conversation

[illegible]

This describes how patients generate, organize, process, and express their thoughts

Examples of disorders: circumstantial thinking (excessive vagueness), ight of ideas (topics are frequently changed), word salad (nonsense words), derailment (irrelevant comments), thought racing or blocking (pressured or halted speech)

[illegible]

The detail of the conversation or content of patients' thoughts, including preoccupations, obsessions, psychotic phenomena, and homicidal or suicidal ideation

Some pain patients have thoughts of self-harm. Risk factors include PD, major psychiatric/medical comorbidities, previous attempts, substance used (alcohol, illicit drugs), and poor social and emotional support, single/widowed, or unemployed

Patients with thoughts of self-harm should be assessed by mental health

[illegible]

Describes the ability of patients to process information

A common cause of cognitive dysfunction is impaired conscious state from underlying medical conditions and adverse reactions from drugs (prescribed, not prescribed, and/or illegal)

One of the most common assessment tools to assess cognitive function is the Mini-Mental State Examination which evaluates concentration, memory, and orientation. A score of 25–30 points is normal. Results indicative of cognitive impairment can be mild (21–24 points), moderate (12–20 points), and severe (<12 points).

[illegible]

It is important to assess for disturbances in perception such as dissociative symptoms (depersonalization, derealization), delusions, hallucinations, and the associated distress

Delusion is an irrational belief that someone has, even sometimes when there is no evidence that the belief is real (e.g. grandiose, passivity, somatic, nihilistic, persecutory, jealousy)

Hallucination is a distortion in a person's perception of reality which is normally accompanied by a powerful sense of reality (e.g. visual, auditory, olfactory, somatic, gustatory)

Insight is the ability of a patient to acknowledge that he/she has a mental health problem, their level of understanding of the treatments available, and the locus of control (internal or external). Also re ects the ability of patients to identify hallucinations, thoughts of self-harm, or other pathological events

Judgement describes the ability to problem-solve, decision-making, and behaviour in that particular context

Insight and judgement can re ect the ability of a patient to manage di culties. This is in uenced by multiple factors such as personal, environmental, cultural, family history, and previous history which can in uence a patient's compliance, rapport, and outcomes

Features of mental state examination associated with psychopathologies in pain patients

Anxiety disorder: apprehensive, dgety, hard to sit still, anxious, irritable

Chronicity: patient looks older than their stated age, poor dentition, poor hygiene, deconditioned physical appearance from the chronic condition

Depression: poorly groomed, unkempt, delusions, poverty of ideas, slow speech, depressed mood, irritable, depressed a ect, withdrawn

Delirium: poorly groomed, unkempt, not cooperative, delusions, thoughts formed in a disordered manner, hallucinations, withdrawn, threatening, unusual behaviour

Dementia: poorly groomed, unkempt, poverty of ideas, cognitive impairment

Mania: agitation, cannot sit down, bright make-up, colourful, strange appearance, disinhibited, delusions, ight of ideas, thoughts formed in a disordered manner, speech rate fast, seductive towards the clinician, threatening

PD: bizarre appearance, scarred wrists, tattoos of not very good quality, not cooperative, seductive towards the clinician, threatening

Psychotic disorder: poorly kempt, staring/bizarre appearance, not cooperative, unusual behaviour

Schizophrenia: unkempt, poorly groomed, delusions, ight of ideas, thoughts formed in a disordered manner, poverty of ideas, hallucinations, blunted a ect, inappropriate behaviour

Substance intoxication or withdrawal: not cooperative, hallucinations, threatening, unusual behaviour, tremors, needle marks in skin

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1.7 Investigations in pain medicine

Introduction

Investigations form the last, but important part of a triad (history, examination, investigations) to formulate a diagnosis

Medical technology has advanced considerably, such that it is easy to evaluate and identify structural abnormalities

However, it is often di cult to correlate the anatomical changes with the patient's symptoms and the degree of functional impairment reported

Functional imaging is the most exciting and rapidly evolving technology to understand the cortical activity for many cognitive processes

Blood tests

Blood tests are often useful for ruling out in ammatory arthritis as a cause for MSK pain

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are often evaluated and found elevated in patients with a strong in ammatory component (see Chapter 25)

Low levels of vitamin D are associated with widespread pain symptoms such as bromyalgia

Other blood tests include thyroid function tests (TFTs), early morning cortisol, and levels of testosterone

In patients who are on long-term opioids (>100 mg oral morphine equivalent dose per day), consider testing for total testosterone and early morning cortisol levels, in addition to other tests, to assess the endocrine system

Imaging techniques

(See Table 1.7.1.)

Objective quanti cation is di cult/impossible for a cognitive phenomenon such as pain

Therefore, imaging should only be used in:

- Presence of red ags
- Severe or traumatic injury
- Suspicion of serious pathology
- Unusual clinical presentations
- Unknown diagnosis following examination
- Injuries that are unresponsive to treatment

Investigations are usually only indicated if the outcome is likely to change treatment and should be discussed on an individual basis

It is often unnecessary to perform expensive investigations to con rm an already obvious clinical diagnosis

Table 1.7.1 Imaging modalities in pain medicine

Electrical activity (increased/decreased excitatory or inhibitory activity, increased/decreased action potentials)	EEG (electroencephalography) EMG (electromyography) MEG (magnetoencephalography)
Metabolic activity (glucose and oxygen consumption)	FDG-PET (uorodeoxyglucose positron emission tomography) Autoradiography
Haemodynamic response (blood ow, blood volume, and blood oxygenation)	H_2O PET (water-based positron emission tomography) NIRS (near infra-red spectroscopy) Optical imaging and fMRI (functional MRI)

X-ray scan

Simple X-rays are useful in acute injury and help in guiding treatment

It uses electromagnetic radiation to produce images of dense tissues such as bone

Computed tomography (CT) scanning

Uses X-ray beams and a computer to produce cross-sectional images of bone and soft tissues

CT uses a signi cant amount of radiation; therefore, MRI is often preferred

CT scans show the bone cortex distinctly, and fractures, loose bodies, and spine changes are better seen

Choice of investigation when patients are tted with a spinal cord stimulator

Magnetic resonance imaging scan

MRI is the most frequently used investigation in pain patients (no radiation is involved)

Fine resolution is achieved in multiple planes; therefore, diagnostic accuracy is excellent

Useful in neuraxial investigations to recognize spinal stenosis, disc prolapse, and nerve root compromise

MRI is commonly used to assess for bone abnormalities, joint abnormalities, soft tissue abnormalities, and nerve root compression, as well as various medical conditions (such as tumours or diseases of internal organs)

Gadolinium enhancement, in addition to MRI, gives better resolution

T1-weighted images: water dark, fat bright (e.g. to assess cortex, fatty tissue, liver lesions) (shorter relaxation time); low signal (dark, e.g. in bone marrow) indicates increased water content and loss of fatty tissue; abnormally low signal indicates pathology (e.g. trauma, infection, cancer)

T2-weighted images: water and fat are bright (e.g. oedema, in ammation, white cortex); abnormally high signal (bright) indicates pathology (e.g. trauma, infection, cancer)

Short tau inversion recovery (STIR) sequence: signal suppression for fat; only water is bright (e.g. in discitis)

If T1 and STIR are compared: abnormally low signal (dark) on T1 and abnormally high signal (bright) on STIR indicates abnormal uid

Fluid-attenuated inversion recovery (FLAIR) images: signal suppression for uid (e.g. cerebrospinal uid (CSF)), used in brain imaging—high signal (bright) shows pathology (e.g. infection, tumour, demyelination)

Few contraindications to MRI: certain brain aneurysm clips, neurostimulators, cardiac pacemakers

Radionucleotide bone scan

Radio-isotopic bone scan or bone scintigraphy is a nuclear scanning test used to detect areas of increased bone turnover such as bone growth or damage (e.g. stress fractures)

It involves injection of a radioactive substance into the body, followed by taking of a series of images using a special camera to detect the radioactive substance (which concentrates in areas where there is increased blood ow and bone turnover such as at fracture sites)

A bone scan is particularly useful for identifying:

- Bone stress reactions
- Bone stress fractures (e.g. navicular, pelvic, pars interarticularis)
- Osteochondral lesions (e.g. osteochondral fracture of the talar dome)
- Other medical conditions a ecting bones (such as bone cancers or bone infections)

Isotopic bone scan is the investigation of choice for evaluating skeletal metastasis

Bone density scan (DEXA scan = Dual-Energy X-ray Absorptiometry)

Used to assess the density (strength) of bones

Indications can be:

- To assess the risk/stage of osteoporosis in patients over 50 years of age
- To assess the risk/stage of osteoporosis in patients aged under 50 years with other risk factors (smoking, drinking, family history of hip fracture, body mass index (BMI) <21)
- Previous bone fracture after minor injury or fall
- Postmenopausal women or after removal of ovaries in women under the age of 45 years (decreased oestrogen levels result in decreased bone density)
- In arthritis or with steroid intake (>3 months)
- May be used to con rm fracture risk to initiate medical treatment

Radiation exposure is much lower than with standard X-rays (however, not recommended in pregnancy)

The scanner is open, and the scan takes 10–20 minutes; the hip, spine, or forearm are scanned

A special type of X-ray is used (DEXA) to measure how much radiation passes through the bones and then compared to a healthy young adult (T-score) or a healthy adult of the same age (Z-score), gender, and ethnicity

The di erence is calculated as a standard deviation (SD)

T-score: above 1 SD is normal; between 1 and 2.5 indicates mildly reduced bone mineral density (BMD); above 2.5 is de ned as osteoporosis

Z-score: below 2 SD indicates that the BMD is lower than expected at a certain age

Ultrasonography

An ultrasound scan (USS) is a painless method of imaging that uses high-frequency sound waves (2–15 MHz)

A probe is usually applied to the skin with the help of a conductive medium (ultrasound (US) gel) to transmit sound waves and assess soft tissues underneath the skin

US is a safe imaging technique as it does not expose the patient to any radiation

Investigation of choice for super cial soft tissue pathology for both diagnosis and treatment

Changes in water content that occur with in ammation and malignant or degenerative processes in muscles, tendons, or tendon sheaths can be detected with USS

One major disadvantage of ultrasound is that it is dependent on the skills and expertise of the operator in question

Unfortunately, US does not provide information on the deeper structures such as joints or bones

Neurophysiology

Neurophysiological tests can be bene cial to investigate some peripheral nerve and root lesions. Also frequently used when there is no clear-cut diagnosis

In subclinical abnormalities, it is important that the results correlate with the clinical picture

Diagnostic tests of the peripheral nervous system; especially useful in evaluating diseases/disorders of the muscles, nerves, and nerve roots (e.g. peripheral nerve palsy)

They record electrical activity of the muscles and the passage of these along nerves in the limbs

Pathological changes and associated disorders can either be acute or have a slow-developing nature

Diagnostic test that evaluates sensory tracts of the central and peripheral nervous systems by recording the electrical responses of the brain and spinal cord to sensory stimulation

Functional biomarkers and network analysis

Biomarkers for pain are actively being researched and will be the future to bring in personalized treatments for patients

Biomarkers can be blood-based or imaging-based around network analysis, fMRI, or magnetoencephalography (MEG)/EEG. This is a fast-evolving eld and of great topical interest

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1.8 Quantitative sensory testing

Introduction

Quantitative sensory testing (QST) is an investigation modality to document the function of smaller nerve bres (in comparison, nerve conduction studies only test large nerve bres, whereas QST could be used to test both large and small nerve bres)

It tests for temperature (small, unmyelinated nerve bres), cold (A- bres), warmth (C- bres), vibration (large, myelinated A- and nerve bres), and touch (A- and bres)

The posterior columns and lateral spinothalamic tract are tested during QST

QST is time-consuming and used more commonly in research trials and longitudinal studies

QST has been used to diagnose diabetic neuropathy, small bre neuropathy, and chemotherapy-induced neuropathy

QST measurement parameters

Allodynia—dynamic mechanical allodynia, punctate mechanical allodynia, pressure-evoked mechanical allodynia, cold allodynia (warmth allodynia is optional)

Hyperalgesia—punctate hyperalgesia

Hyperpathia—this is the clinical equivalent to the 'wind-up' phenomenon

Two-point discrimination

Vibration threshold

Sensory area mapping

To resolve inter-observer variability, the Neuropathic Special Interest Group of the International Society for the Study of Pain (IASP) formulated guidelines in 2013

QST reports

Certain QST findings may relate to specific pathophysiologic mechanisms associated with neuropathic pain: heat hyperalgesia to peripheral sensitization, and static mechanical hyperalgesia or dynamic mechanical allodynia to central sensitization

Thus, it may be useful in differentiating between central and peripheral sensitization

QST has also been used to predict histological small fibre neuropathy in postural tachycardia syndrome

Advantages of QST

Sensory area mapping is possible if the tests are done accurately

QST has shown to be relatively consistent in normal subjects (controls)

Disadvantages of QST

It is a psychophysical test (results will vary, depending on the patient's mood, level of engagement with the test, and the patient's mental condition, including fatigue and drowsiness)

It has large inter-observer variability in patients with neuropathic symptoms (hence, it is not easily reproducible)

Results could vary, depending on the manufacturer of the kit (there is no standardization)

QST cannot differentiate between a peripheral nerve lesion and a central cause since the whole pathway from the peripheral receptor, through the peripheral nerve, to the thalamus, is tested

It has not been used to differentiate between neuropathic and non-neuropathic pain

Additional information

QST has recently been used to differentiate between completers and non-completers of an interdisciplinary pain programme, with maximum differentiation in the temperature thresholds

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1.9 Measurement of pain

Introduction

Pain is a complex, multi-dimensional biopsychosocial phenomenon and its subjective nature makes it challenging to assess and measure

When measuring pain, it is important to consider which aspects of pain information is needed

Scienti cally valid tools are essential to determine the intensity of pain, choose treatment, and assess outcome after treatment

Measurement tools are needed in clinical and research settings to evaluate outcomes after therapy and in pain research

Clinimetrics (= the measurement of clinical phenomena)

1. Scale of pain measurement:
   i. Dichotomous scale (Yes or No)
   ii. Ordinal scale (Mild, Moderate, Severe)
   iii. Interval scale (Visual Analogue Scale (VAS) score)

2. Choice between objective and subjective measurements in pain:
   i. Pain is typically subjective
   ii. Objective measures are not necessarily better than subjective measures
   iii. The scale of measurement is not related to the subjectivity of the measurement

Validity

(= measure of how well a tool measures the construct that it is supposed to measure)

1. *Criterionvalidity*
   This is the most powerful form of validity (the tool is compared to the 'gold standard')

2. *Constructvalidity*
   Next best option when a gold standard is not available (e.g. one measure of pain intensity is compared to another measure with a previously de ned hypothesis)

3. *Contentvalidity*
   It is the degree to which the test measures all relevant items in a given condition

4. *Facevalidity*
   A test appears to measure the construct without paying close attention to the component parts (e.g. VAS pain score has a high face validity)

Reproducibility

Whether the measurement tool provides the same answers when repeated either in time or by di erent observers

There are two types:

Agreement (= lack of measurement error—how close the value of two di erent measurements is in absolute terms)

Reliability (= relative measure, based on the consistency of the measure across di erent conditions and time points, e.g. test–retest reliability, internal consistency, and interrater reliability)

Responsiveness

Parameter for tools that measure change over time, e.g. outcome measures in studies on e ects of a pain treatment

Interpretability

Meaning of a speci c score on a tool, e.g. what a score of 10 on the McGill Pain Questionnaire (MPQ) means

Sensitivity of a measure

Ability to correctly identify the presence of a condition where it exists

Speci city of a measure

Ability to correctly identify the absence of a condition where it does not exist

Choice of outcome measures in research and clinical trials

1. What does one want to know about pain (dimensions and time frame)?
2. Why measure pain?
3. Which instrument is the most appropriate?

1. Pain intensity—Numeric Rating Scale (NRS)
2. Physical functioning—Brief Pain Inventory (BPI) or Multidimensional Pain Inventory
3. Emotional functioning—Beck Depression Inventory and Pro le of Mood States
4. Patient rating of improvement—Patient Global Impression of Change scale

Choice of outcome measures in clinical practice

The Faculty of Pain Medicine (UK) and the British Pain Society released a publication in January 2019, highlighting the most useful outcome measures presently in use in pain clinics in the UK

For each measure, they provide a sense of its validity and reliability, conditions for use, and advantages and disadvantages

Measurements in acute pain

Measurement scales in acute pain are uni-dimensional and designed for the assessment of intensity and degree of pain relief, and the trend is more important than the number (useful in routine post-operative care and in hospital acute surgical or medical care)

Commonly used scales: (0 = no pain; 10 or 100 = worst pain imaginable)

- VAS (usually 0–10 or 0–100)
- NRS (usually 0–10)
- Verbal Rating Scale (VRS: none, mild, moderate, severe)
- Correlation between VRS and NRS: none = 0, mild = 1–3, moderate = 4–6, severe = 7–10

These are reliable, valid measures of intensity of pain and easy to use

NRS is clinically preferred due to its simplicity, while VAS is used in research. VRS is a quick and simple tool, with high validity as an indicator of pain intensity

Acute post-surgical neuropathic pain occurs in 3% of all patients and needs a multi-dimensional tool, e.g. LANSS (Leeds Assessment of Neuropathic Symptoms and Signs), DN4 (Douleur Neuropathique 4), and PainDETECT

Measurements in chronic pain (multi-dimensional scales required)

A 17-item scale, along with 11-point NRS, to assess pain intensity in the preceding 24 hours and 11-point NRS of interference in seven domains of usual activities/functions and mood (site, severity, impact of pain on physical function, mood, sleep, social aspects)

[illegible]

Twenty subgroups of words describing sensory, a ective, evaluative, and miscellaneous components of pain

[illegible]

Eight domains assessing mental and physical functioning and overall health-related QoL (mean score = 50%; >50% is better physical and mental health than mean; <50% worse than mean)

Measurements in neuropathic pain

[illegible]

Seven weighted items:

Five sensory items and two clinical examination ndings.

[illegible]

Nine items:

Six items related to symptoms

Three physical examination ndings identifying pain components

[illegible]

Ten items:

Self-reported tool

Originally distinguished neuropathic lower back pain from mechanical low back pain

[illegible]

Eleven items:

First scale to measure severity of neuropathic pain based on 11 descriptors

Measurements of mood and a ect—anxiety and depression scores

[illegible]

Fourteen items:

Seven items for anxiety and seven for depression

[illegible]

Twenty-one items:

Graded as normal, mild, moderate, severe, and very severe

[illegible]

Seven items:

Score of 0–3 per item (5–9 mild, 10–14 moderate, 15–21 severe)

A score of >10 warrants further assessment ± referral to mental health professional

[illegible]

Nine items:

Score of 0–3 per item to assess severity of depression (0–4 none to minimal, 5–9 mild, 10–14 moderate, 15–19 moderate to severe, 20–27 severe)

[illegible]

Two items:

Score of 0–6, with 3 being the cut-o

Only two items from the PHQ-9 scale, and serves as a screening tool

Measurements of other parameters

[illegible]

Pain Catastrophizing Scale (PCS)—a 13-item scale

[illegible]

Include **Pain Self-E cacy Questionnaire (PSEQ)**:

Assesses con dence in performing daily activities (ten statements relate to daily life on a 7-point scale)

[illegible]

Sixteen items

[illegible]

Thirteen items:

Correlates with development of chronic pain

[illegible]

Measure of QoL; can re ect the overall impact of the condition on the patient's life and the e ect of treatment

[illegible]

Measures ve domains (mobility/self-care/usual activity, pain, and mood) against a 5-point descriptor scale of symptoms/impact intensity

[illegible]

Measures disability level and pain interference with daily activity

Pain Disability Index (PDI)—seven domains

Brief self-assessment of function

It has seven domains which are all assessed on 11-point NRS

Oswestry Disability Index (ODI), version 2.1a

Measure of degree of disability and determines the QoL (minimal, moderate, severe, crippled, bedbound); self-administered

Roland–Morris Disability Index—24-point assessment

Used exclusively for low back pain

Used for assessment of disability; free and easy to use

Pain Self-E cacy Questionnaire (PSEQ)—ten items

Assesses con dence of patients to perform activities while in pain (e.g. for return to work, functional gain)

Patient Global Impression of Change (PGIC)

Assesses all aspects of a patient's health and if there has been an improvement or a decline in clinical status (after treatment or intervention)

Other areas

Memorial Symptom Assessment Scale (MSAS) and its **Short Form (MSAS-SF)**

(See 1.11 Pain assessment in children, p. 36.)

Piece of **Hurt scale** for children aged 3–4 years

Faces Pain Scale for 4- to 12-year olds and VAS (older than 8 years)

Behavioural scales such as **FLACC** (face, leg, activity, cry, and consolability) for post-operative pain

COMFORT Scale for intensive care patients

(See 1.10 Pain assessment in the elderly, p. 32 and 28.7 Pain in the elderly, p. 574.)

NRS and facial pain scales are associated with high completion rate, good concurrence, and acceptable reliability

MOBID-2 can be used for dementia patients

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1.10 Pain assessment in the elderly

Introduction

People over 65 years account for 65% of admissions to hospital, with 40% of the budget of primary care

Prevalence of chronic pain in older people living in the community ranges from 25% to 76%, with those in residential care being higher, ranging from 83% to 93%

Most common sites of pain in older people: back, legs, knees, or hips and 'other' joints

Multidisciplinary approach is essential, but the process can become quite complex due to various challenges

Loneliness and social isolation are strongly associated with increased risk of pain

Signs and symptoms of mood disturbance (depression) and social isolation are strongly associated with pre-existing pain or are a predictor of future pain onset

Pain in the elderly is also covered in 1.9 Measurement of pain—pain scales, p. 27, and in 28.7 Pain in the elderly, p. 574

Challenges in assessment

Attitudes and beliefs in uence all aspects of the pain experience in this age group

Stoicism appears to be more evident in current generations of older people and may contribute to the underreporting of pain (this may not be the case for future generations)

Spouse beliefs can have a negative impact on the development of adaptive responses to chronic pain

Professionals may share or inculcate patients' maladaptive beliefs that hurt equals harm, and consequently recommend or reinforce behaviours such as activity avoidance

Di erences in both patterns and sites have been noted in men and women

Communication

There is a paucity of research regarding the best way of communicating pain information

The level of cognitive impairment should be considered in the assessment of pain

Patients with severe cognitive impairment are unable to self-report pain information

Principles of assessment

1. Assessment of pain information should be multi-dimensional and include eliciting pain treatment information, as well as location and sensory aspects of pain
2. Use of open-ended, rather than closed-ended, questions
3. Do not interrupt when patients are conveying pain information, as this disrupts the amount and nature of pain information conveyed
4. Information regarding prognosis is vital for the elderly (usually only provided in 30%)
5. Assessment of pain can be complicated if the patient has severe cognitive impairment, with communication di culties or language and cultural barriers (observational assessment is required, in addition)
6. Scales that can be used for older patients: **VAS**, **NRS**, **verbal descriptor scale** (presented in large, clear letters/numbers and in good lighting)
7. Patient observation is vitally important to note features such as facial expressions, physical reactions (e.g. guarding, bracing, rubbing the painful area), and negative reactions (e.g. agitation)
8. Pain behaviours are based on individual and clinical judgements, and familiarity with the older person is important in interpreting behaviour
9. Consider including carers in any pain assessment process as they are often more familiar with the subtle changes in the patient's behaviour that indicate pain
10. Self-reporting is the most reliable and valid indicator of pain, even if it is subjective
11. It may be necessary to ask the question in a variety of ways to elicit a consistent response
12. While self-reporting scales are good, they fail to capture uctuations in capacity and pain

Suggested guidance for assessment of pain

1. Assessing for the presence of pain:
   Screening, history, observation, involving families and carers
2. Establish the cause (check for red ags)
3. Multi-dimensional assessment:

Location (self-pointing in cognitively intact older people; pain maps to help locate the site and extent of pain)

Intensity (verbal rating/descriptor scales and NRS for intensity of pain in older people with no cognitive impairment and with mild to moderate cognitive impairment)

Impact of pain and tools for assessment (impact on mood, sleep, mobility, function, and QoL)

Mood (HADS and Geriatric Depression Scale (GDS)—30 items)

Mobility (standardized measure, e.g. Timed-Up-and-Go)

Functional ability (Nottingham Extended Activities of Daily Living Scale or Barthel Index)

Pain assessment tools

No evidence that any one multi-dimensional assessment tool is better than another

All older people in whom pain is detected should have a clinical assessment of the multi-dimensional aspects of pain, including:

A sensory dimension which describes the intensity and nature of pain, e.g. crushing, sharp

An a ective/evaluative dimension which describes the emotional component of pain and how pain is perceived (e.g. dangerous, exhausting, frustrating, frightening)

The impact on life, including physical, functional, and psychosocial e ects

Health care professionals should familiarize themselves with relevant assessment tools and use them routinely

Assessors should consider the use of one tool, or a combination of tools, to assess the di ering dimensions of pain

[redacted]

Pain thermometer = pictorial modi cation of a verbal descriptor scale

No pain (0), slight (1), mild (1–3), moderate (3–5), severe (5–7), very severe (7–9), worst possible pain (10)

[redacted]

A 24-item multi-dimensional pain assessment tool designed for older people

[redacted]

Considered as part of a multi-dimensional assessment of pain in older people

The short form has 15 items that assess severity of pain, interference of daily activities due to pain, and impact of pain on mood and enjoyment of life

[redacted]

Standardized scale for the assessment of pain in cognitively intact adults

Assessment of sensory, a ective, and evaluative dimensions of pain

Pain in older adults with cognitive impairment

A number of behavioural scales have been developed to assess pain in older adults with cognitive impairment (no single instrument can be recommended for general use)

Seven indicators: physiological observation, facial expressions, body movements, verbalizations, changes in interpersonal interactions, activity/routines, and mental status

A hierarchical pain assessment algorithm was proposed that can be utilized either for patients who are self-reporting or for cognitively impaired patients:

Self-report from patient (or reason for not doing it)

Behavioural assessment tools to observe pain behaviours during clinical assessment

Assessment report by the patient's caregivers

List of analgesic trials and non-pharmacologic interventions and their outcomes

Tools for patients with cognitive impairment

In older people with cognitive impairment or with di culty in communication, observational assessment becomes essential for assessing for the presence of pain

Carers familiar with older people with cognitive impairment should be included in the assessment of their pain

[illegible] [illegible] [illegible] SAT

Developed and evaluated in nursing home residents in whom the tool had reasonable reliability and validity

[illegible]

Developed for end-stage dementia; was built based on the DS-DAT

Even though widely used, there has not been adequate critical evaluation

[illegible] 2

French tool developed for multi-dimensional assessment of pain

Includes ten items covering somatic (ve), psychomotor (two), and psychosocial (three) reactions to pain

Most promising tool in terms of evidence

[illegible]

Simple 5-item observational tool, developed and validated in residents with advanced dementia

[illegible]

[illegible]

A 60-item tool covering subtle, as well as common, pain behaviours

[illegible]

Observation of patients' pain behaviours (verbalization, vocalization, face, bracing, rubbing, and restlessness) during activities of daily living (ADL) such as bathing and dressing

Advantages of pain assessment in the elderly

Uncontrolled pain impacts upon the physical health of the older adult and QoL

Therefore, assessment and management of pain are important in all clinical settings

[illegible]

Documentation of our pain management practice

From a professional and legal perspective, we have a duty of care to our patients, regardless of age

In these days of litigation, we could easily become victim of such lawsuits if pain is not recognized and treated appropriately

Research has demonstrated that if pain is assessed appropriately, it can be treated more e ectively and subsequently patients would recover more quickly

Identi cation of treatments that are not working, to raise awareness of e ective and ine ective treatment strategies

Summary

Assessment of pain in older adults can be carried out using the NRS or verbal descriptors, even in the presence of mild to moderate cognitive impairment

There are a number of **behavioural scales** available with high consistency (the most promising in terms of evidence are the Doloplus-2 and PAINAD scales, but the PACSLAC and Abbey Pain Scale are promising in terms of clinical utility)

Observation is an important skill in identifying pain amongst the older population

Sta and caregivers must familiarize with the locally used tools for assessing pain (this will improve the e ectiveness of the assessment tool)

All providers must have structured training in assessment and management of pain in the elderly according to their experience

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1.11 Pain assessment in children

Introduction

Children's pain perception should be an integral part of their pain assessment

This supports Meinhart and McCa ery's statement that 'pain is whatever the person says it is'

It is important to listen to, and understand, the child to create a "child-centred focus"

Challenges in assessment

Previous erroneous assumptions have hampered e orts to assess and manage pain e ectively in children

Prevalent myths supported by the following assumptions:

- Young children are unable to sense pain neurologically
- They do not interpret noxious stimuli as pain
- They do not experience the deleterious consequences of severe pain in the same way as adults

It is now well accepted that anatomical, physiological, and biochemical mechanics needed for pain perception are present early in intrauterine life

In fact, preterm infants can perceive pain in a way comparable to older children

ABCs of pain management

A—Ask about pain regularly. Assess pain systematically

B—Believe the patient and family in their reports of pain and what relieves pain

C—Choose pain control options appropriate for the patient, family, and setting

D—Deliver interventions in a timely, logical, and coordinated fashion

E—Empower patients and their families. Enable patients to control their course

Pain assessment in preverbal population

Recommendations focus on multi-dimensional aspects that are characterized by behavioural and physiological indicators of pain

[illegible]

Developed for post-operative pain, but useful for other pain

Variables to a maximum of 20 points looking at physical and physiological parameters (posture/tone, sleep, expression, cry, colour, respiration, heart rate (HR), saturation, blood pressure (BP), perception of nurses)

<5: nursing comfort, >5: + paracetamol, >10: + opioid

[illegible]

Three behavioural indicators (facial actions for 30 seconds: brow bulge, eye squeeze, and nasolabial furrow), two physiological indicators (HR and oxygen saturation), and two contextual variables (gestational age and behavioural state) that modify pain (each of the seven domains scores 0–3)

0–6: no or minimal discomfort (no action); 7–12: slight–moderate pain (nursing comfort, paracetamol); >12: severe pain (pharmacological measures, e.g. narcotics)

Pain assessment in young infants

[illegible]

Five pain behaviours that make up the scale's name: facial expression, leg movement, activity, cry, and consolability (each behaviour is scored from 0 to 2)

0: comfortable; 1–3: mild discomfort; 4–6: moderate pain; 7–10: severe discomfort/pain

[illegible]

Crying (0–2), facial expression, breathing pattern, arms, legs, state of arousal (all 0–1)

Total score of >3 indicates pain

Pain assessment in school-aged children and adolescents (4–12 years of age)

Several tools are available

In younger children, developmental capabilities may hinder the use of purely numeric scales, and therefore, pictorial-based pain scales, such as the Faces Pain Scale, may be more suitable (e.g. Wong-Baker Faces)

For older children (>8 years of age) who are able to understand abstract concepts, the VAS and 0–10 NRS can be used

Methods to aid the assessment of pain

Q

Question the child (appropriate language, use dolls/toys)

Use a pain rating scale (faces, numeric, behavioural, behavioural/physiological)

Evaluate behaviour and physiological changes (e.g. FLACC scale)

Secure parents' involvement

Take cause of pain into account

Take action and evaluate results

A **vd**

No speech

Limited or absent communication

May have cognitive impairment

Altered body movement

Other pre-existing conditions

Ask carers' opinion

Pn

Spasm/spasticity

Positioning issues

Pressure areas

Bowels

Re ux/gastritis

Surgical complications/late diagnosis

Fear/anxiety/sadness

Environment

Self-report assessment tools

A **—g**

Self-reported tool for pain intensity

Horizontal line, with 'no pain' at one end to 'worst possible pain' at the other

Patient draws a line that intersects to indicate intensity

gW **B** **g** **—g** **g** **a**

Self-reported faces scale for acute pain

Six line-drawn faces, ranging from no pain to worst pain, with a numerical value assigned to each face

It also adds word descriptors to each face (no hurt, hurts a little, hurts a whole lot, etc.)

[illegible]

Self-reported faces scale for acute pain

Six cartoon faces ranging from neutral to high pain expression (numbered 0, 2, 4, 6, 8, and 10)

[illegible]

Self-reported poker chips are used to represent pain intensity

Child chooses which chips represent the pain they experience, with one chip indicating a little hurt and all four chips indicating the most hurt a child could have

Observational assessment tools

[illegible]

(See 1.11 Face, Legs, Activity, Cry, and Consolability (FLACC) Scale, p. 37.)

Five categories of pain behaviours

Simple framework for quantifying pain behaviours in children who may not be able to verbalize the presence or severity of pain

[illegible]

Observational measure of pain and anxiety during invasive medical procedures

Eight de ned behaviours are assessed: muscle tension, screaming, crying, restraint used, pain verbalized, anxiety verbalized, verbal stalling, and physical resistance (scale 1–5)

[illegible]

Observational measure of post-operative pain in children

Six behaviours that include cry, facial, child verbal, torso, touch, and legs (scale of 0–3, based on intensity)

[illegible]

Observer-rated measure for use in intensive care environments

Eight domains thought to be indicative of pain and distress (alertness, calmness/agitation, respiratory response, physical movement, mean arterial BP, HR, muscle tone, and facial tension)

Each domain is scored between 1 and 5, and the scores are added to yield a measure of sedation

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1.12 Pain letter template

Box 1.12.1 shows an example of a structured patient letter.

Box 1.12.1 Structured patient letter

Thank you for referring this … year old gentleman/lady … to the pain clinic. He/she is su ering from …
Referred by …
Patient has been reviewed by the spine surgeon … who does/does not recommend a surgical intervention …
Furthermore, has been seen by … for duodenal ulcer, etc.

Impression

Non-speci c low back pain
Right leg radiculopathy into L5 dermatome (MRI with right L5 foraminal narrowing)

Medication

Pain meds (for how long, how e ective, side e ects)
Other
Allergies/sensitivities

Past medical history

Cardiovascular, respiratory, gastrointestinal, endocrinological (e.g. diabetes), neurological, kidney, or liver comorbidities/problems
Operations (disc, back, joints)
Trauma
Osteoporosis, osteopenia
Vitamin de ciencies (vitamins D and B, folic acid)

Presenting complaint

How long for, sudden or gradual onset (what happened then)
Site/side of pain
Is pain constant, intermittent
Pain intensity (e.g. 0–10/10 on average, range on a good and bad day)
Referred to …/radiating to … (legs, arms), which dermatomes
Pain quality (nociceptive, neuropathic symptoms)
Pain is worse with …
Pain is better with …
Red ags (bladder or bowel problems, recent infection, falls, fractures, night sweats, unexpected weight loss)

Imaging/investigations

X-rays
Ultrasound
MRI scans
CT scans
DEXA scan (bone scan)

PET scan
Other investigations (e.g. gastroscopy, colonoscopy, diagnostic laparoscopy)

Social history

Living with partner/spouse/children/other people
Children (how many and how old)
Profession/employment
Sleep pattern (how many hours per night, waking in pain?)
Impact of pain on daily activities and quality of life (e.g. what does it stop you from doing?)
Previous abuse (physical, sexual, emotional, torture, etc.) if patient happy to disclose

Previous treatments

Physiotherapy (hydrotherapy), massage
Gym/exercises
Warm/cold applications
TENS
Injections
Chiropractor/osteopath
Acupuncture

On examination (chaperone: …), e.g. for lower limb

Lumbar exion, extension, side exion (aggravating pain symptoms?)
Toe and heel walking
(Weakness, numbness)
Power—hip, knee, and ankle exion/extension (myotomes)
Sensory supply (dermatomes)

p

Hip internal/external rotation
Faber's/SIJ stretch tests (supine, lateral, prone)
Piriformis test (if applicable)
Straight leg raise

a

Femoral nerve stretch
Palpation of hips, paravertebral lumbar areas, SIJ, iliac crest (cluneal nerves), piriformis muscle

Plan

(Clear and easy to follow, for example:)

1. Continue regular exercising and stretching. Useful exercises may be swimming, cycling, walking, yoga, pilates …/referral to physiotherapy (e.g. for core exercises)
2. As are-up medication, try … up to four times per day, but not regularly
3. Wean amitriptyline by 10 mg per day at weekly intervals
4. Try nortriptyline, instead of amitriptyline, to be started at 10 mg at night and gradually increased by 10 mg every week, up to a daily maximum as tolerated and needed
5. Lumbar MRI scan ordered
6. Referred to orthopaedics for review
7. Patient may bene t from the attendance of a pain management programme, and referred to …

If you disagree with the content of this letter, or you feel that I have misunderstood you or misrepresented your position, please contact me as soon as possible so that I can issue a correction.
(Copy of the letter supplied to the patient)

Kind regards
Yours sincerely
Dr J Rudiger
Consultant in Pain Medicine

1.13 Mnemonics for referrals

These mnemonics can be useful to request more information from the referrer when a patient is referred to a pain service:

Thank you for referring this patient. Unfortunately, I am unable to accept this patient since your referral letter does not provide enough details about the underlying problem/the reason of the referral.

I would recommend the mnemonic SOCRATES to be able to triage your referral appropriately.

SOCRATES

S—Site/side of symptoms

O—Onset (sudden/gradual, when, constant/intermittent)

C—Character of the pain symptoms (neuropathic, nociceptive, mixed)

R—Radiation (arms, hands, legs, feet) or referral of symptoms (e.g. buttock, shoulder)

A—Associated symptoms (tiredness, fatigue, depression, impact on QoL)

T—Time course/pattern (at rest, with activity)

E—Exacerbating/relieving factors (e.g. lifting, driving, sitting)

S—Severity of pain (e.g. VAS, mild–moderate–severe)

P

Psychosocial background (family, relationship, dependants, employment, stress)

Previous treatments (e.g. injections, physiotherapy, osteopath, chiropractor)

Mental health and addiction medicine

OLD CARTS

O—Onset

L—Location

D—Duration

C—Character

A—Alleviating and Aggravating factors

R—Radiation

T—Treatments

S—Severity

PQRST

P—Provoking factors

Q—Quality

R—Region and Radiation

S—Severity

T—Time

Further reading

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1.14 Waddell's signs

Waddell's signs are a number of physical signs that were rst described by Gordon Waddell in 1980

Intensity of chronic pain is a subjective nding

Pain has been known to be associated with atypical or unexpected symptoms and clinical signs on examination

In the absence of clear diagnostic criteria and a possibility of litigations and secondary gains, it makes it even more complex to diagnose

Neurologists in the late nineteenth century identi ed a group of eight neurological signs which they thought were of non-organic origin, and thus suggestive of malingering

Professor Gordon Waddell, a Scottish orthopaedic surgeon in the 1980s, grouped these eight signs into ve categories:

1. Tenderness (widespread super cial tenderness to light pinch or deep tenderness in non-anatomical distribution)
2. Simulation (based on movements which produce pain, without actually stressing anatomical structures, e.g. lumbar pain with axial loading from the head or pain on simulated rotation)
3. Distraction (rechecking of positive tests when the patient's attention is distracted; for example, a straight leg raise might cause pain when lying down, but a much greater range of pain-free movement may be possible with the same test when sitting)
4. Regional (lower extremity weakness or sensory changes not corresponding to accepted neuroanatomy, e.g. nerve root distribution)
5. Overreaction (subjective signs, such as grimacing, pleading to stop, and tremor, that seem out of proportion to the actual examination)

Waddell suggested that chronic pain patients who are positive in three out of ve categories should have an evaluation for underlying psychological problems

These signs were quite popular and were often used by clinicians on behalf of insurance companies to diagnose malingering

A rigorous evidence-based review suggested that Waddell's signs were organic phenomena, and that they were not associated with secondary gain or psychological distress. This review also suggested that patients with positive Waddell's signs had a higher intensity of pain, displayed reduced functional performance, and had poor outcomes after surgery

There are two important components (regional) of Waddell's signs: the presence of non-dermatomal sensory abnormalities and limb weakness, rather than localized changes

In studies on rodents, it was found that peripheral neuropathies can lead to non-dermatomal sensory abnormalities, while control of pain in humans showed improved hypoaesthesia in limbs. Researchers also suggest that the motor unit ring rates are painful and their synergistic pain-free muscles are inversely proportional to the pain reported by the patient

Waddell's signs are now considered to be of neurophysiological, rather than behavioural, origin and should not be considered to be diagnostic of malingering

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1.15 IASP classi cation of chronic pain for ICD-11

Chronic pain has been recognised as a new diagnosis (disease in its own right)

Chronic primary pain (pain has persisted for more than 3 months and is associated with signi cant emotional distress and/or functional disability, and the pain is not better accounted for by another condition)

Secondary chronic pain (another diagnosis accounts for the presenting symptoms, pain may at least initially be conceived as a symptom secondary to an underlying disease)[4]

Further reading

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SECTION 2

PAIN PHYSIOLOGY

CHAPTER 2

Pain Pathways

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2.1 Peripheral nociceptors

De nitions and introduction

Nociceptors are specialized peripheral dendritic receptors of pseudo-unipolar neurons that encode and transduce noxious stimuli

Nociceptors are sensory receptors of the peripheral somatosensory nervous system

The cell bodies of these pseudo-unipolar neurons are located in speci c ganglia: DRGs, nerve plexuses, CN ganglia (trigeminal ganglion), and nucleus spinalis of the brainstem

Nociceptors are exclusively associated with the extracellular matrix of connective tissues (subcutaneous, fasciae, tendons, organ capsules, periosteum, perineurium, perimysium, periodontium, dura mater, etc.)

No nociceptors are found in the central nervous system (CNS)

Nociceptors develop from neural crest stem cells and are formed during neurogenesis

Anatomy

Nociceptive axons terminate in non-specialized 'free nerve endings'

Nociceptive nerve endings are devoid of myelin sheaths; they branch widely into their target region

A single peripheral axon emanates from the cell body in neural ganglia (DRG, trigeminal ganglion) to innervate the skin and a central axon synapses with second-order neurons (2nd ONs) in the DH of the spinal cord or the trigeminal subnucleus caudalis, respectively

The di erent types of nociceptors are morphologically indistinguishable

The axons associated with nociceptors are A-delta (myelinated, fast, sharper and better localized sensation) and C- bres (unmyelinated, slow, poorly localized sensation)

In the spinal cord, the spinothalamic tract constitutes the major ascending nociceptive pathway

Types of nociceptors

Nociceptors are not uniformly sensitive

They are categorized according to their responses to mechanical, thermal (>40–45°C or <15°C), and/or chemical stimuli liberated by tissue damage, tumour, and/or in ammation

Location: external areas (e.g. skin, cornea, mucosa) and internal areas (e.g. digestive tract, joints, muscle, ligaments)

Skin nociceptors

Four di erent types of nociceptors have been identi ed based on their response to di erent stimuli:

- High-threshold mechanical nociceptors, only responding to intense mechanical stimulation (e.g. pinching, cutting, stretching, pressure)—via A-delta bres
- Thermal nociceptors for cold and heat, also responding to above mechanical stimuli—via A-delta bres
- Chemical nociceptors responding to chemical substances (e.g. cytokines, acids, electricity)—via A-delta bres
- Polymodal nociceptors responding to a variety of high-intensity stimuli (e.g. mechanical, thermal, and chemical substances like the previous three types)—via C- bres

Joint nociceptors

The joint capsules and ligaments contain high-threshold mechanoreceptors, polymodal nociceptors, and 'silent' nociceptors

Many of the bres innervating these nerve endings in the joint capsule contain neuropeptides such as SP and calcitonin gene-related peptide (CGRP)

Visceral nociceptors

Visceral organs contain mechanical pressure, temperature, chemical, and silent nociceptors (many are silent)

The noxious information from visceral organs and skin are carried to the CNS in di erent pathways

Silent nociceptors

In skin and deep tissues, there are additional nociceptors called 'silent' or 'sleep' nociceptors

These receptors are normally unresponsive to noxious mechanical stimulation but become 'awakened' (responsive) to mechanical stimulation during in ammation and after tissue injury

Awakening occurs with continuous stimulation from damaged tissue that reduces the threshold of these nociceptors and causes them to respond

The activation of silent nociceptors may contribute to the induction of hyperalgesia, central sensitization, and allodynia

Physiology

Nociceptors respond to noxious stimuli (extremes in temperature and pressure)

The presence of injured tissue or in ammatory mediators transduces these stimuli into long-ranging electrical signals that are relayed to the brain (the perception of pain is con ned to the brain)

Nociceptors stay sensitized by prolonged stimulation (making them responsive to other sensations as well)

Speed of transmission depends on dendritic diameters and on their extent of myelination: A-delta bres, 2–30 m/s (fast); C- bres: 0.25–1.5 m/s (slow)

It is still unclear whether a single nociceptive neuron can extend neurites equipped with several di erent nociceptors

Nociceptive neurons release a variety of chemical substances from their central terminals to stimulate 2nd ONs

Molecular basis of nociception

Nociceptors are excitatory neurons and release glutamate as their primary NT (as well as SP, CGRP, and somatostatin)

The following substances (in ammatory mediators) are released with tissue damage and can cause nociceptor activation:

> Globulin and protein kinases, arachidonic acid, bradykinin, cytokines, histamine, nerve growth factor (NGF), SP and CGRP, protons (H^+) (low pH), potassium (K^+), PGs, serotonin (5-hydroxytryptamine (5-HT)), acetylcholine (ACh), lactic acid, and adenosine triphosphate (ATP) (subcutaneous (SC) injections of minute quantities of these products excite nociceptors)

Sensation of noxious cold is facilitated by the menthol-activated non-selective cation channel (NSC) TRPM8. Temperature changes activate nociceptors through the cation channel TRPA1

Noxious heat is thought to activate nociceptor membranes through NSC TRPV1

Mechanical and chemical nociceptors are stimulated by various factors, including SP, NGF, CGRP, sodium (Na^+) channels, and transient receptor potential (TRP)-family channels that may become novel targets for therapies

Synapses of nociceptors in DH nuclei show remarkable plasticity, probably important for the development of adaptation and chronic pain

Clinical signi cance

Most nociceptors can be simultaneously stimulated by capsaicin

Local anaesthetics (LAs) aim to block signal transduction in interstitial spaces of connective tissue (e.g. injections of procaine, lidocaine, etc.)

Non-steroidal anti-in ammatory drugs (NSAIDs) act on nociceptors

Anti-nociceptive properties have been described for numerous substances (including cannabinoids). Although they most likely interact with the above-mentioned ion channels, their mode of action is largely unknown

Peripheral neuropathic pain is the result of hyperexcitability of nociceptors after trauma or chronic in ammation

Acupuncture stimulates liberation of opioid peptides from clusters of dermal and interstitial cells (= acupuncture points) to achieve temporary blockade of nociceptors

Naloxone prevents anti-nociceptive e ects of acupuncture

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2.2 Ascending pain pathways

Introduction

There are ascending and descending pain pathways

Nociception is the neural mechanism by which a person detects a noxious stimulus to the periphery

Peripheral nociceptive stimuli are transduced into action potentials (APs), transmitted and modulated along first-, second-, and third-order neurons to higher brain centres where the information is processed and perceived

Nociceptive pathways—transduction, transmission, processing, and perception

Transduction

Physiological process whereby a potentially harmful noxious stimulus (thermal, chemical, or mechanical) is converted into an electrical impulse (AP) by a peripheral nociceptor (see 2.1 Peripheral nociceptors, p. 47)

Peripheral nociceptors are free nerve endings of primary afferent A-beta, A-delta, and C-fibres located in the skin, tissues, or organs

Transmission

First-order neurons (1st ONs)

1st ONs conduct APs from the periphery in a saltatory manner via A-beta, A-delta, and C-fibres (see Table 2.2.1) to the DH of the spinal cord or the medulla oblongata where they terminate and synapse with 2nd ONs (the DRG contains the cell bodies of 1st ONs)

Table 2.2.1 Type of peripheral nerves

Nerve type	Properties	Velocity (m/s)	Function
A-beta (large)	Myelinated	30–70	Touch Pressure Vibration
A-delta (small)	Myelinated	3–30	Pain (pinprick) Temperature (cold threshold)
C (small)	Unmyelinated	0.5–2	Pain (heat/cold/pressure) Temperature (heat threshold)

First-order nociceptive a erents terminate predominantly in super cial layers of the DH (rexed laminae 1 and 2), while non-nociceptive a erents terminate in the deeper layers (lamina 5)

Cell bodies of 1st ONs from the head, mouth, and neck are found in the trigeminal ganglion and transfer APs to the trigeminal nucleus of the brainstem

Second-order neurons

The cell bodies of 2nd ONs are located in the DH of the spinal cord (substantia gelatinosa (SG) or nucleus proprius) and medulla oblongata, and transmit APs to the thalamus, PAG, and RVM by the spinothalamic, spinoreticular, and spinomesencephalic pathways (see Table 2.2.2). (Also see Fig. 20.1.2 in 20.1 Anatomy of the spinal cord, p. 368)

Types of 2nd ONs in the DH:

- Nociceptive-speci c
- Wide dynamic range (WDR) neurons transmit noxious and non-noxious stimuli. Their activity is proportional to the signal intensity and frequency, and they are involved in wind-up and referred pain mechanisms
- Local interneurons (modulate the activity of 1st and 2nd ONs, e.g. inhibitory local interneurons decrease transmission of nociceptive signals from periphery to brain)
- Short projection neurons

Table 2.2.2 Ascending pain pathways

Tract	Location of third-order neuron cell body	Function and nal destination
Lateral spinothalamic	Ventromedial posterior nucleus, medial dorsal nucleus, and ventral post-lateral nucleus of thalamus	Primary somatosensory cortex: sensory and discriminative aspects of pain (intensity, quality, location) Insular and cingulate cortex: memories, emotions, mannerism Hypothalamus: temperature
Anterior spinothalamic	Intralaminar nuclei of the thalamus and reticular formation in the brainstem	Primary somatosensory cortex: crude touch, pressure Hypothalamus, amygdala: a ective aspects such as unpleasantness or fear of pain
Spinoreticular	Medullary-pontine nuclei of the reticular formation	Reticular formation has projections to the thalamus and cerebral cortex which regulate arousal and neural activity in uencing the a ective, emotional, and motivational aspects of pain
Spinomesencephalic	Midbrain tectum and periaqueductal grey area	Midbrain: integration of somatic stimuli with audiovisual information, and emotional and a ective components of pain Periaqueductal grey area: modulation and descending inhibition of painful stimuli
Spinocerebellar	Not present	Cerebellar cortex: proprioception
Fasciculus gracilis and cuneatus	Thalamic ventral posterolateral nucleus	Primary somatosensory cortex: ne touch, pressure, and vibration from levels above T6 by fasciculus cuneatus and below T6 by fasciculus gracilis

Transmission of noxious stimuli from the DH to higher brain centres via ascending pathways is determined by multiple mechanisms and mediators at the pre- and post-synaptic terminals of the spinal cord such as:

- Excitatory mechanisms:
  - Chemicals: CGRP, cholecystokinin, SP, somatostatin, glutamate, aspartate
  - Receptors: -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA), NMDA, glutamate, neurokinin-1 (NK1)
  - Immune system (glia) which secrete chemokines, brain-derived neurotrophic factor (BDNF), IL-1 beta, interferon gamma (IFN-), reactive oxygen species, TNF alpha, intracellular pathways (p38, cyclic adenosine monophosphate (cAMP) response binding element), mitogen-activated protein kinases, SRC family kinases
- Inhibitory mechanisms:
  - Chemicals: gamma aminobutyric acid (GABA), glycine, endogenous opioids, noradrenaline, serotonin
  - Receptors: cannabinoids, opioid, GABA, glycine, serotonin, noradrenaline
  - Local inhibitory interneurons and descending inhibitory pathways activate inhibitory mechanisms which reduce the transmission of noxious stimuli to the brain

Notes on ascending pathways

1st ON cell bodies are located in the DRGs

2nd ON cell bodies are located in the DH (posterior grey horn) of the spinal cord, except for the fasciculus gracilis and cuneatus which are located in the nucleus gracilis and nucleus cuneatus, respectively

Ascending tracts which cross over to the other side of the spinal cord:

- Spinothalamic tracts at the level they enter the spinal cord
- Fasciculus gracilis and cuneatus tracts before joining the medial lemniscus
- Anterior spinocerebellar tracts before entering the spinal cord and then cross again in the cerebellum

Third-order neurons (3rd ONs)

3rd ONs transmit the signals from the nuclei of the thalamus to terminate in higher brain centres (primary somatosensory cortex, cerebellum, anterior cingulate cortex, prefrontal cortex, basal ganglia, amygdala, insular cortex)

There are also projections to the PAG

Pain processing in the brain

Imaging techniques, such as fMRI, have demonstrated that a large brain network is activated during the acute pain experience (cerebral signature for pain, traditionally called the 'pain matrix')

The **'Pain Matrix'** is used to describe areas of the brain activated when someone experiences pain (3rd ONs terminate in the pain matrix):

- Primary somatosensory cortex: conscious information about pain (**intensity, quality, location**) from contralateral aspect of the body
- Prefrontal cortex: integration of sensory messages, memory retrieval, decision-making, and attention processing
- Insular cortex: behavioural and autonomic responses to pain (**memories, emotions, unpleasantness, and mannerisms** associated with pain, leading to negative behavioural and emotional responses)

Anterior cingulate cortex: anxiety, anticipation, attention, and motor responses

Hippocampus, amygdala, and other parts of the limbic system: development and storage of memories related to a ect, emotional events, pain experiences, and the process of learning from these events

The most common areas activated include the primary and secondary somatosensory cortices (S1 and S2), insula, anterior cingulate cortex, prefrontal cortex, thalamus, and limbic system (important areas of pain perception)

Other regions such as the basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices can also be active, dependent upon the individual

In chronic pain, processing mostly involves the limbic circuits, especially the hippocampus, amygdala, and nucleus accumbens, indicating an emotional component involvement

Pain perception

Refers to the process by which a noxious event is recognized as pain by a conscious person

This is complex, and there is no one place within the brain where pain perception occurs

The receptive elds of all pain-sensitive neurons are relatively large, particularly at the level of the thalamus and cortex, because the detection of pain is more important than its precise localization

Treatments used in pain management work by inhibiting the excitatory mechanisms or enhancing the inhibitory mechanisms that modulate the perception of pain

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2.3 Descending pain pathways

Introduction

Ascending nociceptive signals are modulated by the descending pathways

Descending modulation originates in the cortex, midbrain, pons, and medulla. These complex pathways have many interconnections and feedback loops

Descending inhibitory and facilitatory projections travel down the dorsolateral and ventrolateral funiculi of the spinal cord, and terminate in the DH. They facilitate or inhibit nociceptive signal transmission between primary and secondary a erents by modulating:

- Release of neurotransmitters (NTs) and chemicals causing direct pre- or post-synaptic inhibition or excitation, e.g. noradrenaline, serotonin, dopamine, glycine, GABA, endogenous opioids (enkephalins, dynorphins, beta-endorphin), cannabinoids, neurotensin, cholecystokinin, ACh
- Stimulation or inhibition of local interneurons, to inhibit or excite primary and secondary a erents
- Regulate the activity of glia and immune-related mechanisms

Areas in the brain associated with descending modulation

Cortex—somatosensory, cingulate, and insular
Amygdala—located in the temporal lobes, part of the limbic system
Parabrachial nucleus—part of the reticular formation between the midbrain and the pons
Nucleus tractus solitarius—sensory nuclei in the medulla
Rostroventral hypothalamus
Thalamus
Nucleus raphe magnus, RVM—located in the brainstem
Locus coeruleus—located in the pons
PAG—grey matter in the midbrain around the cerebral aqueduct

Pathways associated with descending modulation

Noradrenergic pathways

Originate in the **locus coeruleus and pontine nuclei**
Project to laminae 1, 2, 4, 5, and 10 of the spinal cord DH
Directly stimulate alpha 1 and 2 receptors on pre- and post-ganglionic neurons, and excitatory/inhibitory interneurons
Alpha 1 receptors increase calcium (Ca^{2+}) and reduce K^+ in ux, causing excitation. Alpha 2 receptors have the opposite e ect
Cause inhibition and excitation at the DH

Dopaminergic pathways

Originate from the **periventricular and posterior parts of the hypothalamus**
A ect rst-order a erents and interneurons at the DH
Dopaminergic type 1 and 2 receptors are located on the super cial (1 and 2) and deep (X) laminae of the DH
Cause inhibition and excitation at the DH

Serotonergic pathways

Originate in the dorsal **raphe nucleus, nucleus raphe magnus, and RVM**
Project directly to excitatory and inhibitory interneurons of laminae 2 in the DH
Cause inhibition and excitation at the DH

Periaqueductal grey area

PAG is the grey matter located around the cerebral aqueduct within the tegmentum of the midbrain

Critical structure coordinating descending modulation from supraspinal centres
Receives nociceptive information directly from the DH and indirectly from the thalamus, cortex, limbic system, hypothalamus, nucleus tractus solitarius, and parabrachial nucleus
Main e ect is via activation/inhibition of the RVM and locus coeruleus serotonergic and noradrenergic pathways
It is the main site for action of endorphins and analgesics (opiates and cannabinoids)

Other factors involved in pain modulation

Attention, hypervigilance, observation, empathy
Cognitions (catastrophizing, expectations)
Mood (anxiety, stress)
Genetic factors
Placebo response

Conditioned pain modulation (CPM)

CPM is a psychophysical experimental measure of the endogenous pain inhibitory pathways
CPM is believed to measure the mechanism by which a painful stimulus inhibits/reduces the intensity of further painful stimuli (i.e. the 'pain inhibits pain' phenomenon)
CPM represents the human behavioural correlate of di use noxious inhibitory control which was initially described in rat experimental models
Dysfunctional CPM is common in chronic pain and associated with:
- Decreased central inhibition
- Lower pain threshold
- Development and maintenance of chronic pain

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2.4 Theories of pain

Theories of mechanisms of pain

Theories about pain physiology and its perception have been developing since ancient Greek times. The most famous pain models include the following.

Descartes model

Describes pain as a sensation in the brain resulting from a nociceptive signal being transduced and transported via speci c neural pathways

Speci city theory

Each sensation modality has its own receptor and pathway from the periphery to the CNS

Intensity theory

Any type of stimulus that is su ciently intense can produce a painful signal

Pattern theory

All somatosensory sensations travel via the same type of peripheral receptor and nerve bre, but the rate and intensity of the resulting signal encodes the stimulus type

Gate control theory of pain

Described in 1965 by Ronald Melzack and Patrick Wall

The central idea of the 'gate theory' is the action of interneurons which modulate signal conduction between primary and secondary a erent neurons

Interneurons are inhibitory cells in the SG (grey matter structure of the dorsal spinal cord) which release GABA and glycine to hyperpolarize secondary a erent neurons and reduce or prevent signal transmission to the brain

Theory postulated that the 'gating e ect' of interneurons could be controlled by large myelinated and small unmyelinated bres, which increase or decrease the activity of interneurons, respectively

Non-painful signals transmitted via large A-beta bres stimulate inhibitory interneurons which 'close the gate' to nociceptive signals from C- bres. This prevents conduction of painful signals from primary to secondary a erents and further along to the brain

When nociceptive signals exceed a threshold, large- bre inhibition is overridden by small-diameter bres that reduce interneuron inhibition and 'open' the gate to nociceptive signal transmission to the brain

The 'gate theory' is used to explain the e ects of transcutaneous electrical nerve stimulation (TENS), which stimulates super cial non-nociceptive bres and produces analgesia over the a ected area, as well as using counterstimulation, such as rubbing a painful area, to reduce pain intensity

Integrated models

Neuromatrix model

Incoming sensory information is modi ed by the activity of certain speci c regions of the central nervous system which are collectively called the neuromatrix (brain stem, thalamus, limbic system, prefrontal cortex)

The output from the interaction of the sensory information with these regions results in a "signature of pain" which then de nes the patients pain experience

Biopsychosocial model

Contribution of the psychological and social elements to the experience of pain

First attempt to move away from the previous biological models and theories of pain

Mature organism model

Suggesting that incoming nociceptive signals travel to the brain and are simultaneously compared to a number of other information such as proprioception, interoception, exteroception and cognition

The total sum of the scrutiny of this information results in an output which in a feedback loop in uences further input thus dynamically changing the organisms response to future stimuli and modulating pain.

Bayesian probability theory

Most recent theory that takes into account the concept of predictive processing (Bayesian approach to sensory perception)

This theory helps in accounting for the phenomena of medically unexplained symptoms and the success of placebo treatments

The top down ow of previous brain predictions is met by a bottom up incoming input from any of the senses, and the mismatch between the predicted input and the actual input results in a prediction error which helps the system to revise its initial predictions

A central tenet is that we perceive the world not as it is but our brains best guess, and this is constantly re ned by our senses, both internal and external.

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2.5 Pathophysiology of nociceptive, visceral, and neuropathic pain

Introduction

Nociceptive pain

Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors

Visceral pain

Pain from the activation of nociceptors of the thoracic, pelvic, or abdominal viscera

Neuropathic pain

Pain caused by a lesion or disease of the somatosensory nervous system. It can be further categorized as peripheral or central

Similarities in the pathophysiology of nociceptive, visceral, and neuropathic pain

Some experts believe they are similar entities as they involve similar processes that control signalling of noxious stimuli in the somatosensory nervous system such as:

- Genetic, immune, chemicals, enzymes, and receptors
- Primary a erent nerve—peripheral sensitization
- DH—central sensitization
- Brainstem—dysregulation of the descending pathways that modulate spinal signalling
- Higher brain centres—increased activity of similar mechanisms/areas of the pain matrix

There is an overlap in the response to treatments for di erent types of pain

Low treatment success from lack of speci c pathophysiological mechanisms in di erent conditions

Pathophysiology of nociceptive pain

Involves the transduction of a non-electrical signal to an electrochemical signal

Well localized

Also referred as somatic pain which can be further subclassi ed as:

- Super cial somatic pain—derived from super cial structures
- Deep somatic pain—derived from deeper structures such as muscles, tendons, and joints

Peripheral pathways

High-density innervation

Highly developed thermal and mechanical nociceptors with discrete receptor elds

Mostly via fast A-delta bres which synapse with 2nd ONs at laminae 1 and 5 of the SG of the DH of the spinal cord. Less conduction by C- bres (slower, less myelinated) which nish at lamina 2 of the SG

Small number of collateral neural bres

Central pathways

Fast conduction of nociceptive messages in the CNS

Most travel via the lateral ascending pathways (spinothalamic tract) which transmit well-localized noxious stimuli. A very small number travel by the medial ascending pathways

High topographic representation in the somatosensory cortex and spinal cord

Dominance of the lateral pain system neuromatrix characterized with less emotional responses and better localization of nociceptive messages

Pathophysiology of neuropathic pain

Damage to the nerve pathways at any point from the terminals of the peripheral nociceptors to the cortical neurons in the brain:

- Peripheral: small bres, nerve, plexus, nerve root
- Central: spinal cord, brainstem, thalamus, cortex

Common causes: trauma, ischaemia, haemorrhage, in ammation, neurodegeneration, neurotoxicity, cancer, paraneoplastic, vitamin de ciency, metabolic, autoimmune, hereditary, infection, demyelination, surgery, idiopathic

Development of persistent pain is more common after an injury to a major nerve than after an injury to a non-nervous tissue

Mechanisms of the pathophysiology of neuropathic pain

Injury to a nerve, spinal cord, or brain leads to disinhibition, ectopic discharges, and hyperexcitability

Oedema, increased vascular permeability, and production of in ammatory mediators such as:

- PGs, bradykinin, SP, and CGRP
- Pro-in ammatory cytokines as IL-1B, IL-6, and TNF
- Intracellular phosphorylating mechanisms such as cAMP and protein kinase C

Changes in the structure and function of nerves:

- Ephaptic transmission: adjacent nerve bres are excited by 'non-synaptic cross-talk'. This also happens between somatosensory nerves and nerves of the autonomic nervous system (ANS)
- Expansion of the receptive elds of injured nerves
- Sensory denervation and sprouting of collateral nerve bres
- Upregulation of ion channels (e.g. Na^+, Ca^{2+}, NMDA, glutamate, etc.)
- Phenotypic switch of nerve bres: expression pro-nociceptive mediators (e.g. SP, CGRP) in nerve bres that do not normally transfer painful stimuli such beta bres

In sympathetically mediated pain, there can be vasoconstriction reducing oxygen cell supply, alpha-2 adrenoreceptors expression in a erent sensory bres, denervation, and sprouting of sympathetic bres in the spinal cord

In the CNS, important mechanisms include:

- Increased glutamatergic activity
- Glial activation
- Cortical reorganization as in, for example, phantom limb pain
- Dysfunction of the descending brainstem inhibitory controls, inhibitory neurons at the spinal cord, and production of inhibitory neuropeptides, NTs, receptors, and enzymes

Pathophysiology of visceral pain

Mechanisms in visceral pain, visceral hyperalgesia/allodynia, and referred pain overlap and coexist

Classi cation of visceral pain

Truevisceralpain(tissueinsult): nociception arising from neural sources in deep organs of the body

Visceralhyperalgesia(visceralallodynia): non-noxious stimuli are interpreted as pain due to alterations in nerves carrying visceral sensations at the peripheral and/or central level

Referredpain:

- Viscero-visceral referral: one sensitized organ causes sensitization of another visceral organ
- Viscero-somatic referral: visceral pain causes referred somatic pain
- Somatic-visceral referral: somatic pain causes referred visceral pain

Visceral pain—tissue insult

Poorly localized, di use, and poorly de ned sensation

Visceral bres are not homogenous and transmit painful and non-painful stimuli. For example, vagal bres transmit painful and non-painful sensations (e.g. nausea, hunger, thirst, defecation)

Normally cutting and burning of a visceral structure does not cause visceral pain. Visceral pain can be caused by distension, spasm, traction, ischaemia, and in ammation a ecting the internal organs

Neurohumoral system in uences function and pain from visceral structures—interplay between the ANS, innate and adaptive immune cells, and localized nerve cells

Can be accompanied with motor and autonomic re exes (e.g. nausea, vomiting, sweating, re ex muscle spasm, changes in heart rate and blood pressure)

Peripheral pathways

Wide and overlapping receptive elds

Lower-density innervation as compared to somatic innervation and multiple collateral neural bres

One nerve innervates two visceral organs/structures

Mostly C- bre conduction (slow) and minority by A-delta bres (faster)

Visceral innervation:

- Extrinsic innervation by the ANS via sympathetic bres (sympathetic chain, splanchnic nerves, coeliac, mesenteric, hypogastric plexuses, ganglion impar) and parasympathetic bres (vagal, sacral, and pelvic nerves, and their branches)
- Intrinsic innervation which regulates blood ow, secretions, motility, etc.
- The interaction between extrinsic and intrinsic innervation of visceral structures is not well understood

Poorly developed nociceptors: mechanoreceptors, thermoreceptors, and silent nociceptors. Low-threshold nociceptors are more common than high-threshold nociceptors (3:1)

Central pathways

A erent bres enter the spine via the dorsal root, mostly to super cial lamina 1 and deeper laminae 5–7

Travel in ipsilateral (dorsal columns) and contralateral (spinothalamic) ascending pathways to the brain

Extensive arborization and spread of a erent visceral bres within the spinal cord

Poor representation in the somatosensory cortex—scattered cortical a erent inputs

Dominance of the medial pain system neuromatrix characterized by emotional responses

Visceral hyperalgesia (visceral allodynia)

Normally associated with peripheral and central sensitization

Noxious stimuli in childhood can lead to visceral hyperalgesia later in life

Can develop after and/or coexist with:

- In ammatory conditions (e.g. cystitis, colitis)
- Trauma/stressful situations (e.g. maternal separation, violence, torture)

Stress has an important e ect on the immune system which can lead to visceral in ammation, enhancing visceral permeability and mechanisms involved in visceral hypersensitivity

Autonomic system has an important role; for example, in irritable bowel syndrome (IBS), the enteric nervous system in the abdominal viscera forms the 'second brain'

Some of the pathophysiology mechanisms include:

- Dysregulation of the hypothalamic–pituitary–adrenal axis and raised levels of corticotrophin-releasing factor secretion. This is one of the mechanisms that can lead to visceral hyperalgesia in the absence of a tissue injury in situations such as emotional trauma (e.g. witnessing torture)
- Hyperexcitability and increased responsiveness of the visceral pathways; for example, in studies where the bowel is distended, patients with IBS have higher discomfort than controls
- Neuroplastic changes in the response from visceral a erent pathways and enhanced brain responses to expectations of visceral pain; for example, in pelvic pain, there can be a change in the sensitivity of the mechanosensitive nociceptors in the bladder, a erent and e erent pathways resulting in increased urinary frequency, voiding with a lower threshold, and non-noxious stimuli in the bladder perceived as painful
- Increased sensitivity of the re ex pathways of visceral organs (e.g. defecation re ex after a bowel infection and urinary micturition re ex after a urinary tract infection)
- Neuroimmune mechanisms:
  - Increased activity of glia which produce pro-in ammatory mediators (e.g. TNF alpha and multiple pro-nociceptive mediators)
  - Upregulation of ions, channels, and receptors (e.g. NMDA, glutamate, TRPV1, serotonin)
  - Visceral in ammation promotes visceral hypersensitivity and epithelial permeability. In IBS, mast cells have been found to secrete NGF, serotonin, proteases, and cytokines which excite/promote visceral hypersensitivity.

Referred visceral pain

Viscero-viscero, viscero-somatic, and somato-visceral referral can occur because of:

- Sharing common aspects of their a erent pathways
- Cross-talk between visceral and/or somatic a erent bres

Referred pain can present:

Without hyperalgesia/allodynia. This can occur by visceral somatic convergence (i.e. noxious stimuli travelling from internal organs connect with sensory pathway of somatic organs which are close by). For example, some patients with angina experience referred localized sharp pain radiating down the left arm

With features of hyperalgesia/allodynia, most likely the result of central sensitization resulting from mechanisms such as convergence facilitation and other mechanisms described. For example, in patients who have passed a renal stone, palpation of the super cial skin/muscles ank can make them feel the visceral pain caused by the renal calculus

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2.6 Peripheral sensitization

Introduction

Nociception refers to the perception of noxious stimuli

It is often a protective response and can prevent injury by generating both a re ex withdrawal and enabling behavioural strategies to avoid such stimuli in the future

One such strategy is the sensitization of the nociceptive system such that the threshold for its activation falls and responses to subsequent inputs are ampli ed

Peripheral sensitization

Results in increased/ampli ed nociceptive signals and subsequent input to the spinal cord following persisting in ammation at the peripheral nociceptors either in the viscera or in the skin

If there is no tissue injury, the increased sensitivity usually returns to the normal baseline over time

Nociceptor-induced sensitization of the somatosensory system is adaptive by making the system hyperalert

Sensitization is the expression of di erent forms of functional, chemical, and structural alterations in the nervous system that are mediated by the nociceptor input

The excitation threshold of polymodal nociceptors is reduced to an extent that pain can be elicited by innocuous (normally non-painful) stimuli (allodynia), and pain can be exaggerated and prolonged in response to noxious stimuli (primary hyperalgesia), and it may spread beyond the site of injury (secondary hyperalgesia)

Triggering factors for peripheral sensitization include exposure to **in ammatory mediators** and **damaged tissue**, which change the response of ion channels through the activation of second messenger systems (see Fig. 2.6.1)

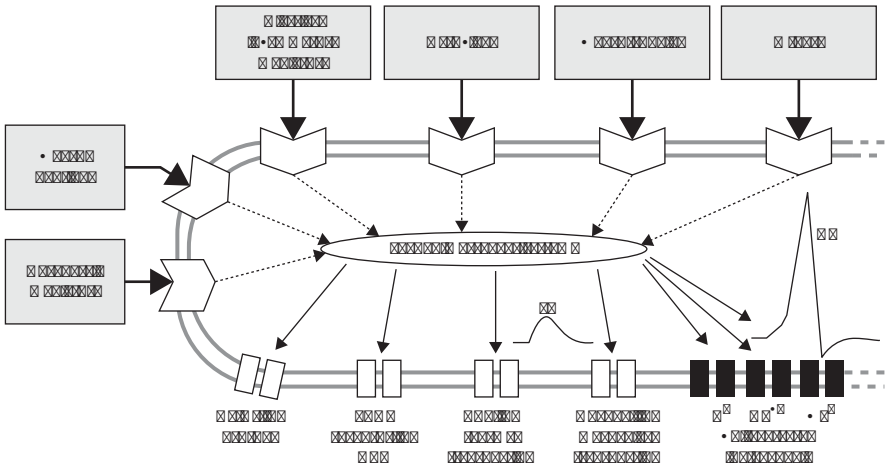


Figure 2.6.1 Schematic drawing of a sensory ending of a nociceptor in the tissue

The membrane at the bottom shows ion channels for transduction (which produce a sensor potential, SP), a voltage-gated Na^+ channel for the generation of action potentials (APs), and voltage-gated K^+ and Ca^{2+} channels that control excitability. Classical in ammatory mediators are bradykinin, prostaglandin E2, 5-hydroxytryptamine, and histamine

ASIC= a cid-sensingionchannel;PTX= purinergicionchannel;TRP= transientr ceptorpotential.

ReproducedwithpermissionfromSchaible,H- G.,Ebersberger ,A.,Natura,G.(2011).Updateonperipheralmechanisms ofpain:beyondprostaglandinsandcytokines.*ArthritisResearch&Therapy*,13(210). https://doi.org/10.1186/ar3305

Di erences between peripheral and central sensitization

Peripheral and central mechanisms di er in terms of the underlying molecular mechanisms

Peripheral sensitization causes sensitization of the nociceptive system and causes in ammatory painful hypersensitivity, and this generally requires ongoing peripheral pathology for maintenance

Peripheral sensitization appears to play a major role in altered heat sensitivity; mechanical sensitivity is a major feature of central sensitization

Silent nociceptors are recruited and this adds signi cantly to the in ammatory nociceptive input to the spinal cord. Resting discharges may be induced or increased in nociceptors because of in ammation, providing continuous a erent signals to the spinal cord maintaining peripheral sensitization

Once peripheral sensitization has occurred, normally non-painful stimuli can cause pain (allodynia)

Peripheral sensitization often leads to central sensitization

Central sensitization does not require ongoing peripheral pathology

In central sensitization, nociceptive neurons in the DHs of the spinal cord are sensitized by peripheral tissue damage or in ammation with subsequent neuroplastic changes, leading to enhanced facilitation and ampli cation of pain signals, which are responsible for the spatial, temporal, and threshold changes in acute and chronic pain states (possible causative mechanism for chronic pain conditions, including allodynia and hyperalgesia)

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2.7 Central sensitization

Introduction

De nition: 'Increased responsiveness of nociceptive neurons in the central nervous system to normal or sub-threshold a erent input'

Central sensitization is an umbrella term used to described changes in the CNS which lead to increased pain perception, due to both increased neuronal excitation and ine ective inhibition

The most commonly described phenomena related to generating central sensitization are long-term potentiation (LTP) and wind-up at the DH:

- Wind-up results from progressive, low-frequency (>0.5 Hz) C- bre stimulation and causes activation of NMDA receptors which increases post-synaptic AP frequency at the DH
- LTP is elicited by high-frequency stimulation and can lead to longer-lasting changes in the DH synapse. The magnitude of LTP is directly proportional to the magnitude of post-synaptic intracellular Ca^{2+} rise
- LTP describes a cellular model of synaptic plasticity, where changes in pre- and post-synaptic neuron structure and function increase the synaptic strength. Practically, this is observed as a rise in post-synaptic current for any given pre-synaptic AP

Central sensitization is likely to occur in the context of an ongoing pain condition. Most patients also commonly experience a host of other symptoms such as fatigue, memory di culties, mood disturbances, appetite changes, and sleep disturbance (no common underlying mechanism has been identi ed to explain the associated symptoms)

Allodynia, hyperalgesia, hyperpathia, hyperaesthesia, or dysaesthesia are clinical features that accompany central sensitization

Aetiology

The mechanisms that lead to the development and persistence of central sensitization are not clearly understood

Patients can develop central sensitization after prolonged and/or repeated noxious stimulation of the DH from ongoing nociceptive, visceral, or neuropathic input (e.g. peripheral conditions such as rheumatoid arthritis (RA) and sickle cell disease, or central conditions such as spinal cord injury (SCI) and malignancy)

In many cases, there is no clear noxious input driving the sensitization process

Many patients with chronic overlapping pain conditions, which include bromyalgia, IBS, temporomandibular joint disorder, chronic low back pain, chronic pelvic pain, tension-type headaches, and migraines, do not have a clear demonstrable physical injury to account for their symptoms. Possible aetiologies of central sensitization in these patients include:

- Single or repetitive stressful events have been linked to acquired or innate changes in nociceptive signal modulation in the spinal cord and the brain
- Genetic susceptibility to central sensitization
- Altered function of the immune, chemical, and electrophysiological systems involved in the perception of pain

Stress, emotions, motivation, cognitions, vigilance, attention, and mood influence the development, persistence, and experience of pain in patients with central sensitization

Long-term potentiation in central sensitization

LTP is a Ca^{2+}-dependent process which leads to increased excitability in second-order nociceptive neurons at the DH

LTP affects synapses of A-delta and C-fibres stimulated at 100 Hz

Changes in both pre- and post-synaptic neurons, such as increase in NTs and numbers/activity of receptors, contribute to the overall increase in synaptic strength

LTP process is facilitated by NMDA (inotropic glutamate channel receptors) and non-NMDA components (NK1 and 2, group 1 metabotropic glutamate receptors, and voltage T-type Ca^{2+} channels)

Rises in post-synaptic intracellular Ca^{2+} activate Ca^{2+}-dependent signal transduction pathways (activation of protein kinase A and C, Ca^{2+}–calmodulin-dependent protein kinase A, phospholipase C, inositol triphosphate (IP3) receptors, nitric oxide (NO) synthase), ultimately leading to:

- Phosphorylation of AMPA receptors and voltage-gated T-type Ca^{2+} channels to lower activation threshold
- Trafficking and insertion of new AMPA receptors onto post-synaptic membrane
- Facilitation of Ca^{2+} release from existing intracellular Ca^{2+} stores

LTP has an early phase, which is independent of *denovo* synthesis and lasts up to 3 hours, and a late phase which involves new protein synthesis and structural synapse changes lasting over 3 hours

Role of wind-up in central sensitization

AP wind-up results from temporal summation of slow synaptic potentials, which leaves insufficient time for 2nd ONs to come back to the resting potential in between stimuli (>0.2 Hz)

The slow (0.5 Hz), repetitive, high-threshold noxious stimulation of C-fibres releases the pro-nociceptive peptides SP and CGRP from primary terminals, which activate NK1 and CGRP receptors on 2nd ONs in the DH

This facilitates activation of NMDA and AMPA receptors by removing the voltage-dependent magnesium (Mg^{2+}) block, boosting post-synaptic AP in a non-linear fashion

Wind-up is reversible and disappears after seconds at the end of a stimulus train (e.g. 30 seconds of stimulation at 2 Hz)

Role of NMDA receptors in central sensitization

Glutamate receptors include:

- Ionotropic receptors: NMDA, AMPA, kainate, and delta
- Metabotropic receptors: group I (coupled with intracellular Ca^{2+} signalling), and groups II and III (negatively coupled to adenylyl cyclase)

The binding of glutamate and glycine to their respective NMDA binding sites allows the displacement of Mg^{2+} from the central ion pore, opening the receptor complex to intracellular Ca^{2+} and Na^{+} influx

The resulting post-synaptic AP activates T-type voltage-gated Ca^{2+} channel opening and activation of multiple Ca^{2+}-dependent pathways (described above in the section of long-term potentiation in central sensitization)

Glutamate also stimulates the release of other pro-nociceptive substances (SP, CGRP, BDNF in the CNS), which decrease synaptic excitability threshold, sensitize 2nd ONs, and activate

wide-dynamic neurons in the DH by non-nociceptive a erent impulses. Other glutamate-mediated changes of the DH synapse architecture and function include:

- Activation of protein kinase enzymes such as JUN N-terminal kinase, mitogen-activated protein kinases (extracellular signal-regulated kinase, tyrosine kinases such as SRC, LYN, and FYN), and p38, which cause:
  - Recruitment of pro-nociceptive receptors (AMPA, glutamate, kainate, NK1, mGlu)
  - Activation of cyclo-oxygenase (COX)-2 and NO synthase generates prostaglandin E2 (PGE2) and NO which promote the release of glutamate and other nociceptive neuropeptides such as SP
  - Activation of protein kinase G1-mediated phosphorylation of IP3 receptors which recruit glutamate- lled synaptic vesicles close to the cell membrane
- Activation of multiple cell nuclear transcription pathways, e.g. c-fos, cAMP response binding element
- Decreased activity of local inhibitory mechanisms:
  - Ca^{2+}-mediated NO synthase-interacting protein and metabotropic glutamate receptor disassembling post-synaptic complexes
  - GABA and glycine as important inhibitory interneurons. Their function is inhibited by:
    - PGE2-driven inhibition of glycine receptor phosphorylation
    - Nerve injury-induced loss of GABA-mediated post-synaptic currents, with loss of potassium chloride channel function

Role of the immune system in central sensitization

Glial cells

Constitute 70% of the CNS

Have a crucial role in maintenance and homeostasis of the CNS

Injury and/or high-threshold activation of 1st ONs release ATP, chemokines (e.g. CC-chemokine ligand), cytokines, and endogenous danger signals (also called damage-associated molecular patterns) which activate glia

Activated glial cells like astrocytes produce pro-nociceptive factors, such as excitatory amino acids (e.g. glutamate), cytokines, and PGs, and reduce the availability of inhibitory NTs (GABA, glycine)

Microglial cells

Under normal conditions, microglia constitute <20% of all spinal glial cells. Nerve injury induces rapid microglia proliferation in the DRGs and spinal cord

Activated microglia are associated with spinal excitation by several mechanisms:

- Increased release of pro-nociceptive substances such as chemokines, cytokines, and cytotoxic substances (NO and free radicals)
- Increased activity of pro-nociceptive receptors (e.g. glutamate receptors such as NMDA)
- Increased activity of excitatory protein kinase enzymes and transcription pathways

Studies have identi ed an immunological mediated 'fear memory' where pro-in ammatory cytokines (IL-1B) secreted by microglia trigger conditioned fear-related memories with associated behavioural responses

Immuno-modulating therapies, such as minocycline and pentoxifylline, decrease the activity of microglia, with positive results in neuropathic pain pre-clinical models (to date, clinical human studies have not been satisfactory)

Role of endogenous pain modulatory systems in central sensitization

Neuroimaging studies (fMRI, PET, proton spectroscopy) have identi ed several potential changes in descending inhibitory pathways, which could be responsible for central sensitization

Structural and functional changes in the anterior cingulate cortex, prefrontal cortex, primary somatosensory cortex, secondary somatosensory cortex, thalamus, and insula have been identi ed in patients displaying features of central sensitization

Dysregulation in the connectivity of di erent structures of the 'pain matrix' include:

- Increased connectivity between the insula and other pain-processing regions not usually involved in pain signalling
- Decreased connectivity between anti-nociceptive regions such as the brainstem, the origin of most descending inhibition pathways
- Decreased activity of the dorsolateral funiculus—the preferred descending inhibition pathway
- Increased activity of descending facilitatory pathways
- Improved connectivity and activity of anti-nociceptive regions, such as PAG, have been found in patients who responded well to to antidepressants that work by serotonin and noradrenaline reuptake inhibition

In the pain matrix and spinal cord:

- Reduced activity of inhibitory NTs (GABA, serotonin, dopamine) and inhibitory receptors (e.g. mu-opioid binding and activity). Clinical studies have shown patients who responded to gabapentinoids decreased their central glutaminergic activity
- Increased activity and concentrations of excitatory NTs like glutamate have been found after noxious and non-noxious stimulation

Role of the endocrine system and autonomic nervous system in central sensitization

Elevated levels of salivary cortisol and CSF corticotropin-releasing factor point to a dysfunction in hypothalamic–pituitary–adrenal (HPA) axis and the ANS

Stress modulation has been shown to normalize cortisol and corticotropin-releasing factor levels in patients who underwent non-pharmacological psychological interventions, as part of their pain management

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CHAPTER 3

Neurotransmitters and Receptors

Ramy Mottaleb, No l Mulla, Maria Stasiowska, and Matthew Wong

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3.1 Neurotransmitters

Introduction

NTs facilitate signal transmission between nerve cells and non-neuronal targets such as muscle cells and glands

NTs are released from pre-synaptic terminals into a synaptic cleft to interact with corresponding receptors on pre-/post-synaptic membranes

Termination of transmission occurs when the NT is removed from the cleft by enzymatic breakdown or uptake into pre-/post-synaptic cells

NTs are synthesized in pre-synaptic terminals, and packaged and stored in vesicles concentrated at the nerve terminal. APs stimulate Ca^{2+} in ux and cause vesicles to move and release their contents into the synaptic cleft by exocytosis

Acetylcholine (ACh)

Synthesis

From choline and acetyl coenzyme A (acetyl-CoA) by choline acetyltransferase

Metabolism

By acetylcholinesterase enzyme into the inactive metabolites choline and acetate at the neuromuscular junction (NMJ) and cholinergic synaptic clefts

Distribution

In pre-synaptic terminals of motor neurons, pre- and post-ganglionic nerve bres of the parasympathetic nervous system, and preganglionic nerve bres of the sympathetic nervous system (SNS) and brain (mesopontine tegmentum, basal ganglia, neocortex, and hippocampus)

Receptors

Nicotinic receptors are ligand-gated ion channels permeable to Na^+, K^+, and Ca^{2+}, located at the NMJ and CNS. Activation cause Ca^{2+} in ux which leads to myocyte contraction or a post-synaptic AP, respectively

Muscarinic receptors are G-protein coupled receptors (GPCRs) in the CNS and ANS supplying the heart, lungs, gastrointestinal (GI) tract, and sweat glands:

- M1, M3, and M5 receptors (G-q) stimulate phospholipase C to generate IP3 and diacylglycerol (DAG), increasing intracellular Ca^{2+} and causing cell excitation
- M2 and M4 receptors (G-i) inhibit adenylyl cyclase and reduce intracellular cAMP and Ca^{2+}

E ects

NMJ: contraction of smooth and striated muscles

Parasympathetic nervous system: lacrimation, salivation, digestion, urination, defecation, and sexual arousal

SNS: activation of sweat glands

CNS: arousal, attention, and memory formation

Other: endothelial muscarinic receptors stimulate production of NO, causing vasodilation

Endorphins

Synthesis

Neuropeptides produced from pro-opiomelanocortin

Metabolism

Metabolized by peptidase enzymes (aminopeptidases, angiotensin-converting enzymes, and serine proteases)

Distribution

Produced primarily in the anterior pituitary gland; however, the precursor pro-opiomelanocortin is extensively distributed in the CNS

Receptors

Mu-opioid receptor agonists activate G-inhibitory proteins, reducing intracellular cAMP and decreasing intracellular Ca^{2+}

Mechanism of action

Produced in the pituitary gland in times of stress, released into the bloodstream, and distributed throughout the body, causing:

- Parasympathetic nervous system—reduction of pain signal transmission at the DH
- CNS—activation of descending inhibition from the amygdala, PAG, reticular formation, and RVM. Also works by increasing dopamine levels in the Mesolimbic Reward System, causing pleasure and reward

Gamma-aminobutyric acid (GABA)

Synthesis

Formed in pre-synaptic terminals of the CNS

The precursor glutamine, stored in glial cells, is converted to glutamate and GABA by glutamic acid decarboxylase (GAD) and pyridoxal phosphate (cofactor)

GABA is packaged into vesicles by vesicular GABA transporter (VGAT) and stored in inhibitory nerve terminals

Excess GABA is broken down in nerve terminals by GABA transaminases (GABA-T) into succinic semialdehyde and glutamate

Metabolism

Removed from the synaptic cleft by transporter proteins into pre-synaptic terminals of inhibitory neurons and adjoining astrocytes

Reuptake into a GABA terminal via GABA transporter (GAT) type 1 (GAT-1) repackages GABA into vesicles using VGAT or breaks it down via GABA-T

Reuptake into a glial cell via GAT-1 or GAT-3 transporters causes intracellular breakdown via GABA-T and conversion to glutamate

Distribution

Throughout the CNS

Receptors

GABA-A: fast-acting ligand-gated ion channel on post-synaptic nerve terminals. Activation causes in ux of chloride and e ux of K^+ ions and hyperpolarizes cell membranes, reducing AP transmission

GABA-A rho (also known as GABA-C): ligand-gated chloride channel and a subtype of GABA-A receptors in the retina

GABA-B: inhibitory G-protein reduces intracellular Ca^{2+} by inhibiting adenylyl cyclase and promoting K^+ e ux. Slower than ligand-gated GABA-A, mediates both post-synaptic and pre-synaptic transmission

Mechanism of action

Principal inhibitory NT in the CNS; reduces neural tone and regulates muscle tension

Serotonin

Synthesis

Serotonin, or 5-HT (5-hydroxytryptamine), is a monoamine produced in the enterochroma n cells of the GI tract where it acts locally facilitating peristalsis, or systemically causing platelet aggregation and vasoconstriction

In the CNS, 5-HT is produced from L-tryptophan (amino acid) transported from the blood to the brain by facilitated transport. L-tryptophan is converted to 5-hydroxytryptophan in serotonergic cells by tryptophan hydroxylase, and nally to 5-HT via L-amino acid decarboxylase

Metabolism

Serotonin is removed from the synaptic cleft by serotonin transporters. Once in the pre-synaptic nerve terminal, 5-HT is metabolized by monoamine oxidase (MAO) and aldehyde dehydrogenase into 5-hydroxyindoleacetic acid (5-HIAA), and is then excreted in the urine

Distribution

CNS: 5-HT is produced in the raphe nuclei and reticular formation, the cell bodies of which project into the spinal cord, cerebellum, and most areas of the brain

Gut: food stimulates enterochroma n cells in the gut lumen to release 5-HT, which stimulates peristalsis

5-HT stimulates the chemoreceptor trigger zone, causing emesis

Receptors

5-HT1 and 5-HT5 are inhibitory GPCRs and reduce intracellular levels of cAMP and Ca^{2+} in post-synaptic neurons

5-HT2, 5-HT4, 5-HT6, and 5-HT7 are excitatory GPCRs and increase the levels of intracellular cAMP and Ca^{2+} in post-synaptic neurons

5-HT3 are ligand-gated cation channels, causing cell depolarization and excitation

Mechanism of action

CNS: controls mood, memory processing, sleep, and cognition. 5-HT3 causes vomiting, anxiety, and seizures

5-HT also mediates gut motility, emesis, vascular smooth muscle tone, and bone metabolism

Noradrenaline

Synthesis

L-tyrosine is actively transported into post-ganglionic sympathetic axons and converted to DOPA by tyrosine hydroxylase (rate-limiting step). DOPA is converted to dopamine by DOPA decarboxylase and transported into vesicles by vesicular monoamine transporter (VMAT). Inside vesicles, dopamine is converted to noradrenaline by dopamine- hydroxylase

Adrenaline is synthesized in cells of the adrenal medulla. The synthesis process is the same as for noradrenaline, with the added nal conversion of noradrenaline to adrenaline via phenylethanolamine-N-methyltransferase

Metabolism

Noradrenaline is removed from the synaptic cleft via pre-synaptic transporter reuptake (UPTAKE 1). Some di uses into the bloodstream and is taken up by extraneural cells (UPTAKE 2) such as the myocardium and smooth muscles

Inside the cells, noradrenaline is either repackaged into vesicles by VMAT or broken down by MAO and catechol-O-methyltransferase (COMT) into metanephrine, dihydroxymandelic acid, and nally vanillylmandelic acid

Distribution

SNS: noradrenaline is the primary NT of post-ganglionic sympathetic nerve bres. It is also released from the adrenal medulla into the systemic circulation, acting like a sympathetic hormone rather than like a NT

CNS: the locus coeruleus contains noradrenergic neurons and projects throughout the brain (brainstem, cerebellum, hypothalamus, thalamus, amygdala, neocortex) and spinal cord

Receptors

GCPRs on cell membranes of the CNS, ANS, and target organs

-2 receptors reduce intracellular cAMP and Ca^{2+}. Located on pre-synaptic terminals of the CNS and ANS, they reduce pre-synaptic NT release

-1 and -1, -2, and -3 receptors increase intracellular Ca^{2+} by activating phospholipase C, increasing levels of DAG and IP3 (-1 receptors) or cAMP (-1, -2, and -3 receptors)

Mechanism of action

Stimulates the CNS to maintain alertness, arousal, and memory. Mediates descending inhibition via -2 receptors in the pre- and post-synaptic neurons at the DH

Outside of the CNS, noradrenaline mediates sympathetic nerve function. -1 receptors on smooth muscles stimulate vascular, sphincter, and visceral contraction. -receptors are widely distributed and mediate chronotropy, inotropy, bronchodilation, and lipolysis

Prostaglandins

Synthesis

Produced by most nucleated cells in the body from essential fatty acids

The main precursor arachidonic acid (AA) is synthesized from diglycerols and phospholipids found in cell membranes, by phospholipase C and A2

AA is processed via the lipoxygenase pathway into leukotrienes, or the COX pathway into PGs

Enzymes in the COX pathway include tonically produced cyclo-oxygenase 1 (COX1) to maintain normal baseline PG production, and cyclo-oxygenase 2 (COX2) induced by stress and in ammation

AA is converted to prostaglandin H2 (PH2) and then into PGD2, PGE2 (dinoprostone), PGF2, PGI2 (prostacyclin), and TXA2 (thromboxane)

Metabolism

Taken into cells by speci c carrier proteins and inactivated in the cytoplasm by 15-hydroxyprostaglandin dehydrogenase

Distribution

Produced throughout the body

Final conversion into speci c PG is at the e ector site:

- PGD2: mast cells and brain
- PGE2: smooth muscle, brain, platelets
- PGF2: smooth muscle
- PGI2: smooth muscle, platelets, CNS, parasympathetic nervous system
- TXA2: platelets

Receptors

GCPRs located on target cell membranes

Receptor activation can cause either cell stimulation or inhibition, depending on the receptor type (Gs/Gq or Gi):

- TXA2, PGD2, and PGE2 have inhibitory and excitatory receptors
- PGI2 and PGF2 have only excitatory receptors

Mechanism of action

Contribute to pain and in ammation; control systemic blood vessel and smooth muscle tone (uterus, GI tract, bronchi, gut, renal vessels), GI secretion, renal function, platelet aggregation, adipogenesis, and protein synthesis

In the parasympathetic nervous system and spinal cord, PGs facilitate peripheral and central sensitization:

- Reduce nociceptor activation threshold
- Increase nociceptor availability on cell membranes
- Increase sensory nerve ending growth and sprouting
- Reduce inhibitory interneuron activity

In the brain, PGs modulate pre-synaptic release and post-synaptic e ects of other NTs (dopamine, serotonin, and noradrenaline)

PGE2 has a direct e ect on the hypothalamus to enhance sympathetic out ow and causes fever

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3.2 Opioid receptors

Introduction

Opioid receptors are inhibitory GPCRs

The term 'opiate' refers to all naturally occurring substances with morphine-like properties derived from the natural alkaloid *Papaversomniferum* (examples are morphine, codeine, and thebaine)

The term 'opioid' is a general term used for synthetic and natural substances that have an a nity for opioid receptors. These include all endogenous neuropeptides (endorphins, enkephalins, and dynorphins), as well as exogenous substances (fentanyl, alfentanil, pethidine, etc.)

Structure of opioid receptors

Glycoproteins found in cell membranes at multiple sites

Highest concentrations are found in the PAG (brain) and SG (spinal cord)

Lower concentrations are found in other areas such as the digestive tract and joints

Members of a large superfamily of GPCRs with:

- Seven-transmembrane receptors
- Extracellular N-terminus
- Intracellular C-terminus
- Heterotrimeric complexes with / / subunits
- Activated by endogenous peptides, as well as exogenous agonists

Molecular mechanism of opioid receptors

Endogenous or exogenous opioids bind to the opioid receptor, producing:

- Pre-synaptic terminal: inhibitory e ect (Gi) closes voltage-gated Ca^{2+} channels and stimulation of K^+ e ux, causing hyperpolarization. Adenylyl cyclase is inhibited, reducing cAMP and preventing the release of pro-nociceptive NTs (noradrenaline, ACh, dopamine) and other mediators such as SP, CGRP, etc.
- Post-synaptic terminal: K^+ channels open and hyperpolarize post-synaptic neurons, inhibiting neural transmission

GABA inhibition pre-synaptically increases dopamine in the nucleus accumbens, initially leading to pleasure/reward. After repeated exogenous opioid exposure, the symptoms of pleasure

diminish and exogenous opioid administration prevents opioid withdrawal symptoms (see 4.5 Tolerance, dependence, addiction, and pseudoaddiction, p. 87)

NMDA antagonism activates serotonin/noradrenergic pathways

Intrinsic receptor activity of opioid receptors

Opioids can be classi ed according to their intrinsic activity at that receptor site:

- Full agonists interact with the receptor to produce a maximal response, e.g. morphine
- Partial agonists bind to receptors to produce a partial response, irrespective of the dose administered, e.g. buprenorphine
- Antagonists bind to the receptor but produce no response, e.g. naloxone
- Mixed agonists/antagonists act as agonists on one or more receptor subtypes and as antagonists at one or more subtypes, e.g. nalbuphine, butorphanol

Opioid receptor subtypes

There are at least 12 pharmacologically de ned opioid receptor subtypes classi ed

Only four opioid receptors have been cloned. Opioid receptors were named based upon their original discovery by the International Union of Pharmacology. Various nomenclatures have been devised since the discovery to name these receptors, some based upon the discovery of 'new' opioid receptors

The three primary receptors that are antagonized by naloxone are named as mu for morphine, delta for vas deferens, and kappa for ketocyclazocine. They have 65–70% sequence homology

Mu opioid receptor

Other names: MOR, OP3, MOP

Endogenous ligand: met-enkephalin, leu-enkephalin, -endorphin

Prototype agonist: morphine

Subtypes: 1, 2, 3

E ects of receptor activation:

- 1 causes supraspinal and spinal analgesia, immune euphoria, urinary retention, locomotion, memory/learning, hypothermia, and hormone secretion
- 2 produces supraspinal and spinal analgesia, respiratory depression, tolerance, constipation, nausea, vomiting, urinary retention, pruritus, miosis, anorexia, euphoria, and dependence
- 3: several roles, including NO release

Kappa opioid receptor

Other names: KOR, OP2, KOP

Endogenous ligand: -endorphin, dynorphin

Prototype agonist: ketocyclazocine

Subtypes: $_1$, $_2$, $_3$

E ects of receptor activation: spinal analgesia, hallucinations, dysphoria, sedation, oliguria, tolerance, dependence, hyperalgesia, neuroendocrine, slowing of GI transit, less respiratory depression compared to mu receptors, oliguria (inhibits antidiuretic hormone (ADH) secretion), and immunological (see 7.1 Overview of opioids, p. 119)

Delta opioid receptor

Other names: DOR, OP1, DOP

Endogenous ligand: leu-enkephalin, met-enkephalin, -endorphin

Prototype agonist: ala-leu-enkephalin

Subtypes: $_1$, $_2$

E ects of receptor activation: supraspinal > spinal analgesia without respiratory depression, facilitates the activity of mu receptor, *thermoregulation,* mood, seizures, dysphoria, psychomimetic e ects, and physical dependence

Orphanin FQ (nociceptin) receptor

Other names: NOR, OP4, NOP

Endogenous ligand: orphanin FQ peptide

E ects of receptor activation: analgesia, associated with less analgesic tolerance, drug reward. Also involved in modulation of pain, behaviour, learning, and memory

Not antagonized by naloxone

Changes in opioid receptors with prolonged exposure to opioids

Decreased receptor activation (desensitization)

Increased receptor phosphorylation

Receptor internalization via endocytosis

Activation of intracellular pro-nociceptive regulatory proteins/enzymes:

Examples: GPCR kinases, -arrestin-2, mitogen-activated phosphorylation pathways

-arrestin-2 knockout mice have been found to have less opioid receptor desensitization, decreased activity of opioid GCPR kinases, enhanced analgesia, and less anti-nociceptive tolerance by opioids. Buprenorphine is associated with less tolerance than other opioids and has been found not to bind/recruit -arrestin-2 receptors

Reduction/inhibition of intracellular regulatory proteins/enzymes:

Example: opioids cause analgesia by inhibiting adenylyl cyclase which inhibits cAMP (cAMP promotes the release of pro-nociceptive NTs and mediators). With prolonged exposure to opioids, inhibition caused by opioids on adenylyl cyclase decreases

Activation of glial cells (astrocytes) by opioids binding to Toll-like receptors (TLRs), mu, and kappa receptors activates/increases neuronal signalling and secretion of pro-in ammatory cytokines (TNF/IL1, IL6)

Prolonged exposure to opioids has e ects on other receptors, with inhibitory actions as NMDA– 2 -1 receptors. Animal studies blocking the NMDA– 2 -1 interaction has reduced opioid-induced hyperalgesia (OIH) and opioid tolerance receptor activation

The above mechanisms are involved in opioid tolerance and OIH (see 2.5 Pathophysiology of nociceptive, visceral, and neuropathic pain, p. 57; 2.6 Peripheral sensitization, p. 61; 4.1 Immunology, in ammation, glia, and pain, p. 79; 4.5 Tolerance, dependence, addiction, and pseudoaddiction, p. 87)

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3.3 Non-opioid receptors

Introduction

Receptors are proteins found throughout the peripheral and central nervous systems

Activation of receptors causes changes within the cell or tissue

By targeting key receptors involved in the transmission of the pain pathways, we are able to potentially o er patients better pain management

Transient receptor potential vanilloid receptor 1 (TRPV1)

Structure: non-selective cation channel

Location: predominantly in the periphery in nociceptors but can also be found centrally

Activators of TRPV1 receptor: heat, physical and chemical stimulation (Ca^{2+} and Mg^{2+}). Initially, upon stimulation, there is increased sensitization with hyperalgesia. Prolonged exposure typically causes desensitization of TRPV1

Function: regulation of body temperature and detection of scalding heat

Drugs acting on the TRPV1 receptor: capsaicin

GABA (-aminobutyric acid) receptor

Structure: there are two main classes. $GABA_A$ are ligand-gated ion channels and $GABA_B$ are GCPRs

Location: CNS, particularly the brain. Approximately 20–50% of all synaptic connections in the brain contain $GABA_A$ receptors

Activators of the GABA receptor: GABA is the endogenous ligand

Function: GABA is the chief inhibitory NT within the CNS, and inhibits neurons to which it binds

Drugs acting on the GABA receptor:

- $GABA_A$: benzodiazepines (BZDs), ethanol, anaesthetic agents, e.g. barbiturates, volatile agents
- $GABA_B$: baclofen

GABAPENTINOIDS DO NOT DIRECTLY ACT ON THE GABA RECEPTOR!

N-methyl-D-aspartate (NMDA) receptor

Structure: glutamate receptor and ion channel protein

Location: pre-synaptic terminals and post-synaptic excitatory neurons

Activators of the NMDA receptor: glutamate, glycine, or serine binds to the receptor, allowing positively charged ions to ow through the membrane

Function: Ca^{2+} ux through the NMDA receptor is important for synaptic plasticity. It plays a role in wind-up and central sensitization

Drugs acting on the NMDA receptor: ketamine, nitrous oxide (N_2O), phencyclidine, Mg^{2+}

Cannabinoid receptor (CBR)

Structure: GCPR with two subtypes (CB-1 and CB-2)

Location:

- CB-1: one of the most common GPCRs in the brain (particularly in the basal ganglia and limbic system). Also found in the lungs, liver, and kidneys
- CB-2: located predominantly peripherally in the immune system, haematopoietic cells, spleen, and peripheral nerve terminals

Activators of the CBR: can be synthetic, plant-based, or endocannabinoids

- Tetrahydrocannabinol (THC): primary psychoactive component and acts by binding to CB-1
- Cannabidiol (CBD): non-psychotropic, little a nity to CB-1 or 2 receptors, has neuroprotective and anti-in ammatory e ects, modulates ascending and descending pathways

Function:

- CB-1: appetite, nausea and vomiting, mood, pain, memory
- CB-2: in ammation, pain modulation

Drugs acting on CBRs: nabilone, Sativex®, CBD oil

Alpha-2 receptor

Structure: GCPRs with three subtypes (-2A, -2B, and -2C)

Location: -2A and 2C subtypes are found mainly in the CNS. -2B receptors are found mainly on vascular smooth muscle, but also in the CNS

Activators of -2 receptors: endogenous agonists include noradrenaline and adrenaline as part of a feedback loop. All three subtypes have been shown to inhibit adenylyl cyclase, which decreases cAMP, causing hyperpolarization of noradrenergic neurons. This leads to neuronal suppression and inhibition of noradrenaline release, reducing ascending noradrenergic pathways

Function:

- Suppression of ascending noradrenergic pathways causes sedation and hypnosis
- Stimulation of -2 receptors in the DH inhibits nociceptors and the release of SP
- The negative feedback loop may cause reductions in HR and BP, and attenuation of the sympathetic stress response

Drugs acting on -2 receptor: clonidine, tizanidine, dexmedetomidine

Serotonin (or 5-HT) receptors

Structure: seven receptor subtypes. All are GCPRs, except 5-HT3 which is a ligand-gated ion channel

Location: blood vessels, central and peripheral nervous system, platelets, smooth muscle, and GI tract

Activators of serotonin receptor: serotonin

Function:

- Pain modulation: has a role in both excitatory and inhibitory pain pathways, as well as contributes to hyperalgesia
- Receptor activation modulates the release of SP and NTs such as glutamate, GABA, dopamine, noradrenaline, and ACh. 5-HT1A, 5-HT2A, 5-HT3, and 5-HT7 receptors are implicated in most with pain states

Other functions include mood regulation, emesis, cardiovascular and respiratory autoregulation, addiction, appetite, and sexual behaviour

Drugs acting on serotonin receptors:

- Atypical antipsychotics: olanzapine, risperidone
- Tricyclic antidepressants (TCAs): amitriptyline, nortriptyline
- Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and noradrenaline reuptake inhibitor antidepressants: citalopram, duloxetine, uoxetine
- Opioids: tramadol

Glycine receptor

Structure: ligand-gated ion channels

Location: CNS, including the brainstem and spinal cord. Predominantly post-synaptic

Activators of the glycine receptor: glycine opens the glycine receptor, causing an in ux of chloride ions, which hyperpolarizes the post-synaptic cell, inhibiting neuronal ring

Function:

- Mediates fast inhibitory neurotransmission
- Controls a variety of motor and sensory functions, including vision and hearing
- In laminae 1 and 2 of the DH, it inhibits the propagation of nociceptive signals to higher brain regions

Drugs acting on the glycine receptor: cannabinoids

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CHAPTER 4

Neurobiology of Pain

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4.1 Immunology, in ammation, glia, and pain

De nitions

Glial cells: most abundant cells in the CNS, providing support to neurons, but not conducting electrical impulses, e.g. oligodendrocytes, astrocytes, ependymal cells, Schwann cells, microglia, satellite cells

Microglia: these are quiescent immune cells of the CNS; when activated, can phagocytose, present antigen to T cells, and produce cytokines

Astrocytes: specialized glial cells of the nervous system that perform multiple homeostatic functions for the survival and maintenance of the neurovascular unit. Astrocytes have neuroprotective, angiogenic, immunomodulatory, neurogenic, antioxidant properties, and modulate synaptic function

Neuropathic pain: pain due to lesion or disease of the somatosensory nervous system

Common causes of neuropathic pain

Post-herpetic neuralgia (PHN) after a herpes zoster infection, painful diabetic polyneuropathy, trigeminal neuralgia, post-amputation pain, persistent post-operative or post-traumatic pain, pain in cancer patients and HIV patients

Association between activation of microglial cells in response to nerve injury and development and maintenance of neuropathic pain

Multiple studies have suggested that the immune system is involved not only in neuropathic pain conditions, but also in most chronic pain conditions, and drives the acute to chronic pain transition

Opioids activate glia, which are involved in opioid tolerance and OIH. Mu-opioid agonists activate innate immune receptors, and not the classic opioid receptors, creating neuroin ammation by binding to myeloid di erentiation protein 2 (MD-2), an accessory

protein of Toll-like receptor 4 (TLR4). This induces TLR4 oligomerization and triggers pro-in ammation

What happens then?

At site of nerve injury

1. Nerve injury results in recruitment of resident and blood macrophages with the chemokines CCL2 and 3
2. Activated macrophages and denervated Schwann cells secrete metalloproteases, which attack the basal lamina of endoneural blood vessels, causing interruption of the blood–nerve barrier
3. Nerve injury causes the release of vasoactive mediators from injured axons, i.e. SP, CGRP, bradykinin, and NO, causing **hyperaemia and swelling of neurons**
4. These processes further support the invasion of macrophages, T lymphocytes, and mast cells at the lesion site and DRG, and in the ventral and dorsal roots of the spinal cord
5. Within minutes of injury, neuregulin, a growth and di erentiation factor on the axonal membrane, induces activation of ERBB2 (a tyrosine kinase receptor), which helps in **Schwann cell proliferation**
6. Schwann cells release the chemical signals NGF and glial cell line-derived neurotrophic factor (GDNF), which promote axonal growth and remyelination, and also **sensitize nociceptors**, initiating pain in response to nerve injury
7. Schwann cells, macrophages, mast cells, and neutrophils release pro-in ammatory cytokines ILs (1 , 6, 12, 18), TNF, and interferon gamma (IFN-), which cause **axonal damage and modulate nociceptor sensitivity**

At dorsal root ganglion

1. Peripheral nerve injury triggers the release of the chemokines CCL1 (fractalkine) and CCL2, which further **triggers the invasion of macrophages**, supported by locally present macrophages and T cells
2. The density of macrophages increases in the DRG 1 week after injury and remains elevated for at least 3 months, after which macrophages then turn into active phagocytes, removing debris from injured sensory neurons
3. This persistence of the immune response in the DRG contrasts with the peripheral reaction which ends with removal of myelin debris during Wallerian degeneration
4. The signalling pathway that modulates neuronal and macrophage function in the DRG involves purinergic (P2) receptors, activated by ATP release from injured nerves and surrounding tissue. Nociceptors predominantly express P2X and P2Y receptors in macrophages
5. These P2 receptors are responsible for increasing nociceptor sensitivity and activity, **causing hypersensitivity to mechanical and thermal stimuli**, also mediated by voltage-gated Na^+ channels, which are activated by cytokines (TNF, IL1, IL6) released by macrophage activation
6. The cytokine IL6, in association with NGF and neurotrophin-3 from satellite cells, is also responsible for **triggering sprouting of sympathetic bres** around large-diameter sensory neurons (A-beta)

In spinal cord

1. Microglial cells are key in the in ammatory response to direct injury of the CNS in icted by trauma, ischaemia, autoimmune disorders (multiple sclerosis (MS)), and neurodegenerative disorders

2. Microglia form dense clusters around the dorsal and ventral horns after neuronal injury. The process involves **recruitment and activation** of microglia by di erent pathways, leading to neural in ammation
3. Three signalling pathways mediate **recruitment of microglia and circulating macrophages** at the spinal cord level:
   - Chemokine fractalkine, a neuronal transmembrane glycoprotein
   - CCL2
   - Mammalian Toll-like receptors (TLRs) involved in initiation of innate immunity against invading pathogens
4. Activation of microglia involves binding of ATP, released from injured primary and DH neurons, to the purinergic receptor P2RX4
5. Activation of microglia initiates the process involved in **central sensitization**:
   - Release of BDNF which prompts reversal of inhibitory GABA currents, causing **mechanical allodynia**
   - Enhanced spontaneous and evoked excitatory post-synaptic potential (EPSP)
   - Glutamate release in the DH, **activating NMDA receptors**
   - Increased synthesis of lysosomal proteases, ILs, and TNF, which cause direct modulation of the DH in the spinal cord
   - Proliferation and activation of astrocytes, which are responsible for **prolonged or sustained sensitization of the DH**

New treatment opportunities

1. Currently, most anti-neuropathic drugs aim to reduce the excitability of neurons in the peripheral nervous system or CNS, without a ecting glial plasticity, which is responsible for initiation of the cascade, leading to the development of established neuropathic pain
2. Current therapy targeting glial cells mainly involves anti-in ammatory (propentophylline, pentoxyfylline, methotrexate, minocycline) or anti-metabolic (uorocitrate, uoroacetate), which can be counterproductive as it may a ect normal glial cells, which have vital housekeeping and surveillance functions
3. More targeted interventions aimed at purinergic receptors and CBRs, mitogen-activated protein kinase (MAPK), TNF, and ILs
4. CBR2 receptors are expressed primarily by immune cells, including microglia and astrocytes, and may be the target to avoid glial plasticity

Conclusion

Contribution of immune and glial cells to the development of acute and persistent neuropathic pain challenges the concept of neuronal involvement only in the development of neuropathic pain

Animal studies direct us towards the concept of neuronal in ammation, and further studies are required to correlate the in ammatory markers in the periphery, DRG, and DH with the incidence of acute and chronic neuropathic pain

Therapies directed at prevention of neuropathic pain after injury by modulating neuroglial plasticity may be the target for future treatment strategy

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4.2 Genetics and pain

Background

Pain is a very subjective experience, and everyone is unique in their perception and response to pain

As a complex trait, pain is polygenic and shaped by environmental pressures

Genetic contribution to pain perception is about 50%

Basic overview

What is a gene?

Genes are parts of deoxyribonucleic acid (DNA) molecules that contain the information used by cells to construct protein molecules. They code for proteins and it is these proteins that carry out work of the cell such as enzymatic action, motility, and electrical impulse generation

What is a pain gene?

A 'pain gene' is a gene for which there are one or more polymorphisms, i.e. variations in the sequence of DNA base pairs that a ect the expression or functioning of its protein product in a way that a ects pain response

How do DNA polymorphisms a ect pain?

In the human genome, at least 99.9% of a base pair sequence is identical from one person to the next. The remaining 0.1% represents about 3 000 000 base pairs that might di er amongst individuals

DNA polymorphisms can be in the form of single nucleotide polymorphism (SNP) or sequence polymorphism occurring in the sequence of DNA base pairs that actually encodes the protein, i.e. in exons, which might destroy the protein's function completely or alter it in more subtle ways, including enhancing its function

Sequence polymorphisms can also occur in nearby regions of the DNA molecule that regulate the 'expression' of a pain gene

Such variants might a ect how much of the gene product is synthesized without having any e ect on the structure or function of the protein product itself

A DNA sequence polymorphism can also a ect the 'bar code' address of a gene's protein product, the part of the sequence that tells the cell where speci cally to send this particular protein molecule

If the protein molecule is not sent to the correct part of the cell ('tra cking error'), pain processing may not work properly

Examples

$Na_v1.7$ Na^+ channel (*SCN9A*)—protein with direct relevance to excitability of sensory neurons

Erythromelalgia—gain-of-function mutation

Paroxysmal extreme pain disorder—gain-of-function mutation

Congenital insensitivity to pain—loss-of-function mutation

Fibromyalgia

Speci c genetic polymorphisms involving the serotonin 5-HT2A receptor, serotonin transporter, dopamine 4 receptor, and COMT have been reported more frequently in patients with bromyalgia

Finding the pain genes

Linkage analysis

Useful in large families where some individuals develop the painful condition and others do not

Useful in single-gene mutation of major e ect ('Mendelian gene')—Charcot–Marie–Tooth (CMT) neuropathy, erythromelalgia

Limited to diseases that arise spontaneously and not well suited to painful conditions that arise following injury or disease such as low back pain, diabetic neuropathy, or phantom limb pain

Association studies

Comparing the genomes of large cohorts that differ in the trait of interest but are as similar as possible with regard to other parameters such as environment and ethnic background

Two alternative strategies: (1) testing for allelic di erences in a small number of 'candidate genes' selected on the basis of prior hypotheses on where the di erences might lie; (2) searching for potential di erences in all genes and regulatory regions in a hypothesis-free manner (genome-wide association studies (GWAS))

Use of genetics

Diagnostic and prognostic information—a genetic polymorphism may indicate that a particular individual is prone to post-surgical pain and this information can be useful to perioperative physicians and surgeons

Pharmacogenetics—study of genetic di erences in response to analgesic drugs can help in individualizing pain treatment to speci c patients

Contribution to patient–clinician relationship—since pain is very subjective, genetics may help in better understanding without labelling people as malingerers or complainers

Understanding of pain mechanisms

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4.3 Gender and pain

Background

Women and men di er in their responses to pain, with increased pain sensitivity and risk of clinical pain commonly observed amongst women

The di erences in clinical and experimental pain are attributed to several biopsychosocial mechanisms

Gender di erences in clinical pain and experimentally induced pain

Women report pain more frequently than men

The population prevalence of several common chronic pain conditions is greater in women than in men, including bromyalgia, migraine, chronic tension-type headache, IBS, temporomandibular disorders, and interstitial cystitis

Regarding pain severity, the ndings are less consistent and are likely in uenced by multiple methodological factors, including selection biases in clinical studies and the potential for sex di erences in the e ects of pain treatments

The direction of sex di erences in pain responses across multiple experimental stimulus modalities and pain measures is highly consistent, with women showing greater sensitivity than men

However, the magnitude (and statistical signi cance) of sex di erences varies across measures, as it does across published studies

Gender di erences in response to pain interventions

Greater 'analgesic' e ects were observed for women using patient-controlled analgesia (PCA) with morphine

In clinical studies, women exhibit greater analgesia than men in response to mixed action opioids, e.g. butorphanol, nalbuphine, pentazocine

Several studies suggest that di erences in pain treatment between women and men are in uenced by both patient and provider characteristics, an e ect which may lead to disparities in pain management

Responses to non-pharmacological treatments may di er for men and women; for example, when patients were asked to focus on the sensory components of pain, men reported less pain than women, whereas when they focused on the a ective components of pain, women reported more pain than men

Mechanisms of gender di erences in pain

Interaction among biological, psychological, and socio-cultural factors probably contributes to these di erences

Biological factors

In uence of sex hormones represents an important source of pain-related variability

There is evidence suggesting sex-related cortical di erences during the processing of pain-related stimuli, thus potentially implicating the in uence of sex hormones on di erential brain activation

There are also ndings which suggest that the interactive e ects of the opioidergic system with gonadal hormones may be an important determinant of sex-based di erences in pain sensitivity

Testosterone appears to be more anti-nociceptive and protective in nature, especially given the association between decreased androgen concentrations and chronic pain

The e ects of oestradiol and progesterone on pain sensitivity are relatively complex as both exert pro-nociceptive and anti-nociceptive e ects on pain

Pain perception varies according to the menstrual cycle phases in women with chronic pain perception, with patients rating pain signi cantly higher in some phases of menstrual cycle than in others

Fibromyalgia symptoms are associated with the luteal phase, when both oestrogen and progesterone levels are high

Psychological factors

Increased prevalence of depression and anxiety in females, compared to males, is a likely contributor to the gender di erence in pain perception

Women are known to catastrophize more than men, and this involves magni cation and self-rumination of pain-related information

Pain coping strategies are di erent between men and women:

- Men tend to use behavioural distraction and problem-focused tactics to manage pain
- Women tend to use a range of coping techniques, including social support, positive self-statements, emotion-focused techniques, cognitive reinterpretation, and attentional focus

Socio-cultural factors

Social factors, such as gender role expectations, stereotypes, and cultural di erences in pain-related beliefs, play an important role in gender di erence in pain across various cultural and ethnic backgrounds

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4.4 Stress and pain

De nition

Stress response is amongst the functional properties of the limbic system

The axis of central (hypothalamic) and systemic (pituitary and adrenal) stress response is a physiological cascade, essential for survival (HPA axis)

Systemic stress response includes increased serum levels of adrenal gland hormones

Perception and cognition of pain is a brain function (neuropathic pain), not necessarily linked to activation of peripheral and central nociceptors (nociceptive pain)

Pain is a potent stressor

Chronic stress and depression are closely linked

Endocrine basis

Glucocorticoids (GCs) are released from the adrenal cortex in response to pituitary adrenocorticotrophic hormone (ACTH), which is released in response to corticotropin-releasing hormone (CRH) from the hypothalamus

GCs are steroid hormones that have multiple genomic e ects through nuclear receptors

GCs have anti-in ammatory, and therefore indirect, analgesic e ects due to their ability to block cytokine release and to control oedema

GCs are likely to have direct inhibitory actions on nociceptors via membrane receptors

In response to stress, adrenal medullary monoamines (adrenaline, noradrenaline) are released, which modulate the sympathetic nervous system

Neuroanatomy of the stress–pain axis

Nociceptors in the DRG and their ascending fibre tracts reach specific nuclei of the posterior thalamus. Their projections terminate in the post-central gyrus

Thalamo-cortical projections are the basis of cognition

The cingulate cortex is the port of entry of nociceptive inputs into the limbic system, which is the activator of central stress response

GCs cross the blood–brain barrier (BBB) to modulate the central pathways of pain

The reticular formation (RF) in the brain and spinal cord is part of the pain modulatory system. It is activated upon stress response

The dorsal portion of the RF enhances nociceptive responses

The ventrolateral part of the RF has anti-nociceptive properties

Neuroplasticity is thought to be the cause of adaptation to pain and its link to stress response

Inflammation

Inflammation is caused by the liberation of cytokines that can be blocked by GCs

Cytokines can induce changes in neurotransmitter metabolism, neuroendocrine function, and neuroplasticity

Inflammatory stress activates the HPA axis

Clinical relevance

Intense acute stress has analgesic effects: perception of pain seems to be impaired in patients under shock

Chronic stress and chronic depression are frequently linked to chronic pain. These three symptoms seem to potentiate each other. The underlying mechanisms are still largely unclear

Sensation of pain is increased (altered) in depressed patients

Cytokines activate nociceptors

Central and peripheral nociceptive pathways express opioid receptors. Their ligands play an important role in therapy of both depression and chronic pain

Monoamine transmitters (e.g. serotonin) and their receptors in the limbic system are pharmacological targets for treatment of both chronic pain and depression

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4.5 Tolerance, dependence, addiction, and pseudoaddiction

Tolerance

Predictable physiological phenomenon where drug exposure diminution of e ect, or where higher doses are required to produce the same e ect

Innate tolerance

Genetically determined

Acquired tolerance

Pharmacokinetic tolerance: due to changes in drug metabolism and distribution after repeated administration, i.e. enzyme induction and receptor desensitization

Pharmacodynamic tolerance: drug-induced changes in receptor density

Speci c to opioid tolerance

Functional decoupling of opioid receptors from G protein-regulated cellular mechanisms (see 3.2 Opioid receptors, p. 72)

Downregulation of endogenous opioids or opioid receptors

Behavioural changes

Selective tolerance

Tolerance to di erent opioid side e ects develops at di erent rates

Tolerance to euphoria, respiratory depression, sedation, nausea, and vomiting develops rapidly

Tolerance to constipation and miosis is minimal

Cross-tolerance

Tolerance to other drugs within the same class

Opioids have incomplete cross-tolerance due to di ering opioid receptor subtype a nity

NMDA antagonists may block the anti-nociceptive tolerance to morphine

Dependence

Predictable physiological phenomenon where repeated exposure produces changes in gene expression

Physical dependence

Seen with chronic drug use where reduction/discontinuation results in drug-speci c withdrawal symptoms

Psychological dependence

A lot of drugs can produce it, but not all will produce dysfunctional behavioural patterns

Opioid dependence

Neuroplastic changes not fully reversible, contributing to susceptibility to relapse upon opioid re-exposure

Unpleasant withdrawal symptoms usually occurring at 2–5 days, making patients unwilling to discontinue opioids

The International Classification of Diseases, 11th Revision (ICD-11) diagnostic criteria: '*The features of dependence are usually evident over a period of at least 12 months but the diagnosis may be made if opioid use is continuous (daily or almost daily) for at least 1 month*'

Addiction

Unpredictable phenomenon complicated by genetic, environmental, and psychosocial factors

Maladaptive behaviours: impaired control, craving, continued and compulsive use despite physical, social, and psychological harm

Quick to relapse into addiction after a period of abstinence

Risk factors

Family history of drug dependence, lack of employment, lack of stable social and family relationships

Implicated neurobiological mechanisms

Homeostasis theory (disequilibrium between positive reward of drug and subsequent negative reinforcement)

Incentive salience theory (sensitization of dopaminergic mesolimbic reward system and dysfunction of modulating systems → craving)

Habit theory (learnt behaviour)

Pseudoaddiction

Iatrogenic syndrome of behavioural changes that may occur when pain is undertreated—patients may request or seek additional medications (legally or illegally) due to being prescribed insufficient drug doses

Patient demonstrates similar drug-seeking behaviours:

- Drug hoarding
- Attempts to obtain extra supplies
- Doctor-shopping
- Requests for early prescriptions and increased dosages
- May even resort to illicit drug use

Common occurrence is switching from parenteral to oral dose of opioid—where dose is thought to be equivalent but is insufficient

Main distinguisher between addiction and pseudoaddiction: in pseudoaddiction, the inappropriate behaviour ceases once pain has been treated

Additional information

Confusion between dependence and addiction:

- Dependence = requiring drug to prevent physical withdrawal syndrome
- Addiction = continued use of a drug despite harmful effects

Opiophobia is the phenomenon of failure to administer opioids due to fear of addiction developing

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4.6 Neurobiological and physiological changes in response to drug misuse

Substance misuse disorders were once viewed as a character failing but are now considered to be chronic illnesses, associated with comorbidity, social dysfunction, impaired voluntary control, poor compliance, and behavioural issues.

Risk factors for addiction

Genetic factors may account for up to 70% of individual di erences. Genes involved in strengthening neuronal connections, as well as those involved in alcohol and nicotine metabolism, have been associated with addiction risk

Psychological make-up

Environmental and socio-cultural factors

Mental health problems

Poverty and poor support network

Three-stage vicious addiction cycle

Binge/intoxication stage

Mediated at the basal ganglia level, speci cally the nucleus accumbens (pleasure/reward e ect: dopamine-/endogenous opioid-mediated) and the dorsal striatum (habit formation: dopamine-/glutamate-mediated)

Withdrawal/negative a ect stage

Mediated by activation of 'stress systems' in the extended amygdala (NTs: corticotropin-releasing factor (CRF), noradrenaline, and dynorphin), accompanied by diminished activation of the basal ganglia's dopamine reward systems

The individual then tries to alleviate the negative emotional state by compulsive drug use

Third stage (preoccupation/anticipation)

Deterioration in judgement and executive control ('stop' and 'go' systems) caused by a compromised prefrontal cortex

It is driven by glutamate overactivity and promotes impulsive and compulsive drug-seeking behaviour

Opioids

Attach to speci c opioid receptors in the brain, causing the release of dopamine in the nucleus accumbens, which leads to euphoria, respiratory depression, analgesia, and sedation

Chronic exposure causes a cycle of intoxication, tolerance, escalating use, and nally withdrawal

Opioid withdrawal manifests as physical and psychological features: body aches, increased pain, sweating, abdominal cramps and diarrhoea associated with profound agitation, emotional distress, tearfulness, anxiety, and low mood

Result in intense cravings

Alcohol

Interacts with GABA and glutamate NT pathways, leading to euphoria, sedation, reduced anxiety, and motor impairment, including cravings, negative emotions, and withdrawal symptoms

Cannabis

Causes increased dopamine release in the basal ganglia

Due to the longer half-life of THC, cannabis users typically do not smoke it as frequently as tobacco

The interaction of cannabis with endogenous cannabinoid NTs results in distortion of motor coordination and time perception

Stimulants (cocaine, amphetamines)

Increase dopamine levels in the brain's reward centres, resulting in a euphoric 'high' and increased focus on tasks, which is why stimulants are prescribed for attention-de cit hyperactivity disorder (methylphenidate, dextroamphetamine)

The release of noradrenaline results in sympathetic stimulation

Results in binge intoxication, followed by a crash and then intense cravings

Synthetic drugs

They work through the above NT systems as well but are more potent and therefore result in more intense cravings and withdrawals

Some, such as MDMA (*3,4-methylenedioxy-methamphetamine*) and LSD (lysergic acid diethylamide) also work through serotonin pathways to produce changes in perception ('trips')

MDMA also alters mood and perception, and increases the activity of dopamine and noradrenaline

LSD is hallucinogenic, causes anxiety and depression, and activates the CVS

Mental illness and addiction

Over 40% of individuals have a concurrent mental illness

Schizophrenia is associated with a high incidence of smoking, and PTSD with alcohol overuse

Drug use provides individuals with mental illness a temporary 'escape'

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SECTION 3

PHARMACOLOGY

CHAPTER 5

Basic Principles of Pharmacology

Nishi Patel and Kathleen Shelley

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5.2 Pharmacokinetics 94

5.1 Agonists and antagonists

Basic terminology

Ligands

Any substance which binds to a receptor is known as a *ligand*
Ligands that activate a receptor to produce a biological response are called *agonists*
Ligands that block agonist-mediated responses are called *antagonists*

Drug-receptor interaction

A nity and intrinsic activity (IA) determine the pharmacological e ect of a drug
A nity—describes how avidly a drug binds to a receptor
IA—refers to the magnitude of response once the drug is bound:
- IA value of 1 = 100% response
- IA value of 0 = 0% response
- IA value of 1 = 100% opposite response to agonist (inverse agonist)

Agonists

Characteristics

High a nity to the receptor
Full IA

Classi cation

Endogenous agonist—naturally present in the body, and binds to and activates a receptor
Full agonist—activates the receptor and produces full e cacy equal to that of the endogenous ligand (IA = 1) (see Fig. 5.1.1)
Super agonist—produces a greater response than the endogenous agonist (IA >1)
Partial agonist—binds to and activates the receptor, but only with partial e cacy relative to a full agonist (IA <1). Can act as an antagonist if it prevents full agonist binding to the receptor
Inverse agonist—binds to the receptor, inhibits normal activity, and exerts the opposite pharmacological activity (IA = 1)

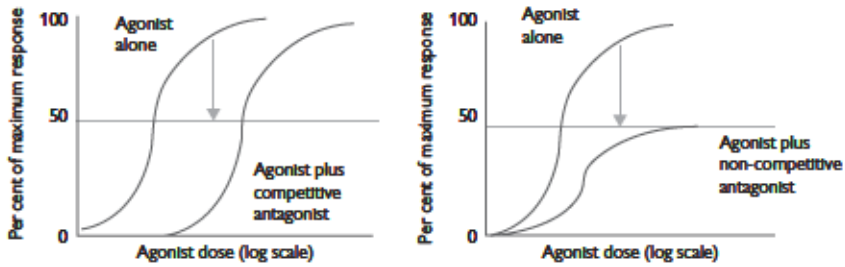


Figure 5.1.1 Dose–response curve: effect of antagonists on agonists

Antagonists

Characteristics

- High affinity to the receptor
- No IA = 0

Classification

- *Competitive antagonist*:
  - Binds to the receptor in a reversible way without activating the effector system for that receptor
  - In the presence of a competitive antagonist, the log dose–response curve is shifted to the right (i.e. higher dose of agonist required to produce the same maximal effect)
- *Non-competitive antagonist*:
  - Binds to a different site on the receptor and causes a conformational change to prevent agonist binding
  - Cannot be overcome by increasing the concentration of agonists

Examples

- Receptor = mu-opioid receptor
  - Full agonist = morphine, fentanyl, codeine
  - Partial agonist = buprenorphine, butorphanol
  - Mixed agonist = pentazocine
  - Antagonist = naloxone, naltrexone

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5.2 Pharmacokinetics

- Pharmacokinetics describes the absorption, distribution, metabolism, and elimination of drugs

Basic principles

Drug passage across the cell membrane

Drugs need to pass through one or more cell membranes to reach their site of action:

- Cell membrane = 10 nm bilipid layer
- Contains glycoproteins which act as ion channels, receptors, intermediate messengers (G proteins), or enzymes

Crossing mechanisms

Passive di usion—most common; drug di uses down a concentration gradient
Facilitated di usion—rate of di usion is enhanced by transport proteins
Active transport—requires energy and pumps against the concentration gradient
Pinocytosis—invagination of drug in membrane

Determinants of di usion

Surface area
Molecular weight
Concentration
Ionization: unionized form will cross the bilipid layer

- pKa is the pH at which a drug is 50% unionized and 50% ionized
- pH = pKa + log (proton acceptor (alkali))/(proton donor (acid))
- pH = pKa + log (aH)/(a)
- Acid environments shift the equation to the left
- Alkaline environments shift the equation to the right
- A weak acid in an acidic environment will remain mainly in its unionized form, therefore greater membrane crossing
- In an alkaline solution, a weak acid will remain trapped as it is ionized
- Acidic drugs—if pH < pKa = greater unionized concentration and greater absorption, e.g. aspirin in the stomach
- If pH > pKa, then a greater degree is ionized
- A weak base in an alkaline solution—a greater concentration is unionized
- A weak base in an acidic solution—a greater concentration is ionized

Protein binding

A ects the duration of e ect
Only unbound drugs have an e ect—therefore, caution in states of low protein concentration

Absorption

Absorption is passage of a drug from the site of drug administration into plasma
The rate and extent of drug absorption depend on the route of administration

Routes of administration

Enteral

Oral:

- Drug is absorbed in the stomach or small bowel (mainly passive transfer), then enters the portal venous system and passes through the liver, before gaining access into the systemic circulation
- A ected by:

- Drug factors:
  - Drug particle size and formulation, e.g. slow release
  - Physicochemical, i.e. interaction with another compound; for example, tetracycline precipitates with Ca^{2+}
- Patient factors:
  - Relation to a meal—slower absorption of drug post-meal
  - GI motility, e.g. gastric stasis
  - GI pH, e.g. strong bases poorly absorbed in acidic stomach and GI tract
  - Splanchnic blood ow
  - First-pass metabolism—the drug passes into the portal circulation from the gut and is metabolized by the liver, therefore reducing the concentration available systemically

Buccal/sublingual/rectal:

Some drugs introduced into the alimentary tract are absorbed directly into the systemic circulation without passing through the liver, thereby avoiding metabolism by gut wall or liver enzymes (rst-pass metabolism):

- Rectal:
  - If drug is inserted lower down in the rectal passage, it enters the inferior rectal vein, to the pudendal vein and the inferior vena cava, and avoids rst-pass metabolism
  - If drug is inserted higher up, it enters the middle and superior rectal veins which lead to the portal veins, and undergoes rst-pass metabolism
  - Absorption is a ected by the proximity to faeces
  - Contraindicated if recent bowel surgery, rectal pain, diarrhoea, or immunocompromised

Parenteral

This includes any route that avoids absorption via the GI tract such as administration by injection or inhalation or by application to the skin

- IV:
  - Fastest and most certain route of administration
  - Peak concentration depends on the rate of administration
- Intramuscular (IM)/SC:
  - Depends on perfusion to injection site—heat can increase perfusion by 30%
  - Overdose risk in shocked patients with poor perfusion—often given repeated doses, which risks a high drug load when perfusion improves
- Intranasal:
  - Avoids rst-pass metabolism, except for any fraction that is swallowed
  - Particle size needs to be <1 micrometre in order to enter the alveoli and bloodstream
- Transdermal:
  - Advantages:
    - Controlled absorption
    - Constant concentration
    - Avoids rst-pass metabolism
    - Can improve compliance
  - Disadvantages:
    - Not all drugs suitable
    - Reduced absorption if shocked
    - A ected by temperature
    - Expensive

Skin irritation
Slower onset of action and titration—this is not a desirable property for medications used in acute pain management

Drug:
Needs to be low molecular weight (<500 Da)
Low melting point (liquid on the skin)
Unionized
Potent—low volume
Hydrophilic and lipophilic
Short half-life (t1/2)

Epidural/intrathecal:
Delivers drug close to the spinal cord at low doses
Single shot or infusion

Bioavailability

Bioavailability (BA) = the fraction of a drug dose which reaches systemic circulation, compared with the IV dose (see Fig. 5.2.1)

This is, in turn, a ected by:
Preparation
Ionization—highly ionized molecules have low BA
First-pass metabolism

Distribution

In uences

Lipid solubility:
pK
pH
Protein binding—a ects free concentration of the drug
Regional blood ow
Speci c property of the drug

Volume of distribution (Vd)

The theoretical volume into which a drug distributes following its administration

$$Vd = D/C_0$$

where D = dose, C0 = concentration at time 0

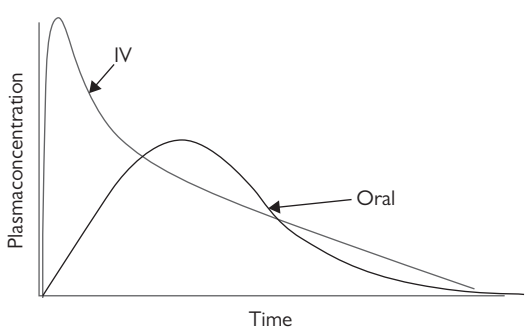


Figure 5.2.1 Bioavailability of drugs

Vd = volume of water in which an injected dose would have to be diluted in order to give the measured plasma concentration

Vd = blood volume for a drug con ned to plasma, e.g. warfarin

Vd = total body water volume for a drug that distributes throughout the body, e.g. theophylline

Vd > total body water for a drug that is concentrated in the tissues, e.g. chloroquine

In general, drugs with high polarity and those that are highly protein-bound and highly ionized have lower Vd

Vd may be altered in disease states such as renal failure (uid retention) and liver failure (altered body uid and protein binding)

Compartment modelling have been devised to further explain the distribution of drugs in the body

Metabolism

Process by which drugs are chemically transformed (usually in the liver) from a lipid-soluble form, suitable for absorption and distribution, to a more water-soluble form that is suitable for excretion (usually by the kidneys)

Usually reduces drug activity unless it is a prodrug, e.g. diamorphine

Non-liver sites of metabolism include the lungs, kidneys, and GI tract

Performed by zero- and rst-order kinetics (see Fig. 5.2.2)

Metabolism—phase I

Non-synthetic/functional reactions:

- Oxidation (mostly)
- Reduction
- Hydrolysis

Mainly in the endoplasmic reticulum of the liver by cytochrome P450 (see below)

Also in the lungs, GI tract, brain, and kidneys

Metabolism—cytochrome P450:

- Superfamily of iron-containing enzymes
- >70 isoforms
- Pigmented pink, hence 'P', and peak absorption of light is at 450 nm in the presence of carbon monoxide

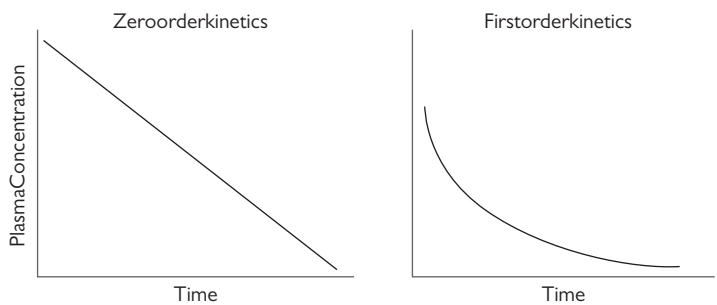


Figure 5.2.2 Zero- and rst-order kinetics

Important in metabolism of a number of endogenous and exogenous compounds
Mediates the majority of phase I reactions
Predominantly found in the smooth endoplasmic reticulum of the liver and small intestine
Divided into families according to structure, e.g. CYP1, CYP2
Clinically important—CYP2D6 and CYP3A4:
Enzyme induction, e.g. anticonvulsants, barbiturates, alcohol, smoking
Enzyme inhibition, e.g. amiodarone, cimetidine, uoxetine

Metabolism—phase II

Synthetic reactions
Molecules of phase I metabolites (or, in some cases, unchanged drug) combine with an endogenous substrate to form an inactive conjugate that is much more water-soluble than the phase I metabolite:
Glucuronidation
Methylation
Sulphation
Acetylation
Also in plasma, e.g. by plasma cholinesterases (ester LAs) and by non-speci c esterases (remifentanil)
Genetic polymorphisms a ect metabolism (e.g. codeine)

Excretion

Process by which drugs are removed from the body, the route of which is largely determined by the molecular weight and structure of the drug
Most common routes of excretion:
Urine—particularly for low-molecular weight drugs (depends on glomerular ltration rate (GFR)/water solubility)
Bile
Also via:
Saliva and sweat
Faeces (larger-molecular weight drugs)
Expired air
Breast milk

Renal excretion

Mechanisms of renal excretion:
Glomerular ltration of drugs which are:
Small
Ionized
Free (not protein-bound)
Active transport and secretion in proximal convoluted tubules (PCTs)
Di usion into distal convoluted tubules (DCTs):
Can be increased by alkalinizing urine, e.g. TCA overdose
Renal failure:
Risk of drug accumulation due to impaired excretion
Drug dose = dose × (impaired clearance/normal clearance)

Biliary excretion

These are often larger-molecular weight compounds (>30 000 Da) and are actively excreted from hepatocytes into the biliary canaliculus against a concentration gradient

May re-enter enterohepatic circulation

Bile > small bowel > reabsorbed into the portal circulation > liver > re-excreted into bile or back into systemic circulation

Presence of small bowel bacterial glucuronidase can render some conjugates lipid-soluble and hence reabsorbed

Liver failure:

- Complex pharmacokinetic implications, including:
  - Reduced protein binding (from decreased protein synthesis)
  - Decreased metabolism (phase I and II reactions)
  - Increased Vd (ascites)
  - Reduced hepatic clearance and increased BA (from porto-systemic shunts)
- Care with BZDs and opioids in encephalopathy

Elimination

Relationship between rate of drug elimination (R_{elim}) and plasma drug concentration

Limited by enzymes and carrier-mediated processes which can become saturated at supratherapeutic doses

- First-order kinetics:
  - R_{elim} is dependent and proportional to plasma drug concentration (simple exponential process)
  - System exhibits excess capacity
  - Most drugs eliminated in this way
- Zero-order kinetics:
  - R_{elim} occurs at a constant rate and is independent of plasma drug concentration
  - First-order kinetics may become zero-order when the elimination system is at saturated capacity, e.g. aspirin, phenytoin, ethanol

Clearance (Cl) and rate of elimination (R_{elim})

Clearance = *volume of plasma* cleared of a drug per unit time (mL/min)

- $Cl = K_e \times Vd$
- Cl = elimination rate constant (min^{-1}) × Vd (mL)
- Used to measure drug elimination by metabolism ± excretion
- Also used to determine the rate of elimination below

Rate of elimination = *amount of drug* removed per unit time (mg/min)

- $R_{elim} = Cl \times Css$
- R_{elim} = Cl (mL/min) × plasma concentration at steady state (mg/mL)
- Used to determine the rate of drug administration

Further reading

1. Peck TE, Hill SA. Pharmacology for Anaesthesia and Intensive Care. 3rd edition, 2008. Cambridge: Cambridge University Press

CHAPTER 6

Local Anaesthetics

Enrique Collantes, Kavita Poply, and Jan Rudiger

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6.1 Local anaesthetics

Introduction

LAs cause reversible blockage of Na^+ channels, blocking the transmission of APs across nerve cells

The function of sensory and motor nerve bres are a ected to di erent degrees by LA, depending on the:

- Anatomy of the nerve bres
- LA properties (concentration, pKa, volume), route of delivery, pH balance, and use of other agents that alter the duration and onset of action of LAs

Classi cation

LAs are broadly divided into two categories, based on the linkage between the aromatic (lipophilic) and amine (hydrophilic) groups:

- Esters (O-C-O), e.g. procaine, tetracaine, cocaine
- Amides (CO-NH), e.g. lidocaine, prilocaine, bupivacaine, ropivacaine, dibucaine

Mechanism of action

A resting membrane potential (RMP) of 80 mV is maintained across the neuronal cell membranes by:

- Na^+/K^+ ATPase activity which keeps a 30-fold K^+ concentration gradient inside, and a 10-fold Na^+ concentration gradient outside, the cell membrane
- Intracellular anionic proteins preventing leakage of K^+ outside the cell membrane

In the resting state, nerve cell membranes are impermeable to Na^+ ions

An AP is generated as follows:

- A chemical/electrical trigger alters the permeability of Na^+ channels
- When the intracellular cell membrane reaches 55mV, voltage-sensitive Na^+ channels open. The AP is conducted across the cell and the membrane potential across the neuronal cell membranes reaches +30mV
- Finally, Na^+ channels close, with K^+ e ux restoring a RMP of 80 mV

LAs block Na^+ channels, stopping the transmission of AP across nerve cells as follows:

Unionized form (lipid-soluble) of LAs passes through the membrane. The ionized form of LAs binds to the internal surface of Na^+ channels, resulting in prevention of Na^+ entry inside the cell, causing hyperpolarization

An alternative theory describes that LAs dissolve in the cell membrane, causing expansion and inactivation of Na^+ channels

Physiochemical characteristics

Weak bases

Water-soluble hydrochloric salts containing sodium metabisulphite and fungicide preservatives

Only subarachnoid preparations are preservative-free

At physiological pH, LAs remain in ionized forms as their pKa is higher than the pH:

Lidocaine has a pKa of 7.9 and a neutral pH of 7.4

$pH = pKa + \log[B/BH^+]$

$7.4 = 7.9 + \log[B/BH^+]$

$0.5 = \log[B/BH^+]$

$0.3 = [B/BH^+]$

Therefore, at physiological pH, lidocaine is 25% unionized (B) and 75% ionized (BH^+)

Onset of action, duration, and potency

These factors are dependent on individual LA chemical structure (see Table 6.1.1)

Potency is related to:

Lipid solubility—the more lipid-soluble, the higher the potency

Intrinsic vasodilator properties—a ect the amount of available LA at the site

Duration of action has a direct relationship with the protein-binding capacity

Table 6.1.1 Doses, onset, and duration of action of local anaesthetics

	Lidocaine	Prilocaine	Bupivacaine	Levobupivacaine	Ropivacaine
Description	Amide	Amide	Amide	Amide	Amide
Relative potency	2	2	8	8	6
Onset	5–10 minutes	5–10 minutes	10–15 minutes	10–15 minutes	10–15 minutes
Duration (without adrenaline)	1–2 hours	1–2 hours	3–12 hours	3–12 hours	3–12 hours
Duration (with adrenaline)	2–4 hours	2–4 hours	4–12 hours	4–12 hours	4–12 hours
Maximum dose (without adrenaline)	3 mg/kg	6 mg/kg	2 mg/kg	2.5 mg/kg	3 mg/kg
Maximum dose (with adrenaline)	7 mg/kg	9 mg/kg	2.5 mg/kg	3 mg/kg	4 mg/kg

Onset of action has an inverse relationship with the pKa. At physiological pH, the higher the LA's pKa, the more ionized form of the LA is present and the less ability to penetrate the cell membrane to act upon the ion channel, leading to a slower onset of action, while the converse is true with low pKa. In an acidic environment (e.g. infected abscess), LAs work less, as a greater ionized fraction is present, not allowing penetration of the LA across the cell membrane

Other agents can be added to some LAs:

- Adrenaline or felypressin slows down the absorption from the site of injection, hence prolonging the duration of action
- Bicarbonate alkalinizes the pH, resulting in a higher proportion of LA in the unionized preparation, hence increasing the onset of action

Pharmacodynamics

Cardiovascular system

Lidocaine can be used to treat cardiac arrhythmias. It blocks cardiac Na^+ channels, hence decreasing the maximum rate of increase of phase 0 of the cardiac AP

PR and QRS intervals are prolonged

Direct myocardial depressant activity (bupivacaine > lidocaine), with the potential to develop re-entrant arrhythmias and ventricular fibrillation due to prolonged binding to Na^+ channels

Tachycardia further potentiates frequency-dependent blockade by bupivacaine, hence resulting in cardiac toxicity. Ropivacaine (propyl substitution for the butyl group of bupivacaine) S-enantiomer is less cardiotoxic due to rapid dissociation from the cardiac channels. However, ropivacaine is less potent and has a shorter duration of action than bupivacaine

Central nervous system

LAs cause reversible neural blockade. Administration of LA to the CNS (e.g. in LA toxicity) leads to a biphasic effect:

- Initially, there is rapid onset of an excitatory phase due to blockage of inhibitory interneurons. This leads to circumoral tingling, visual disturbances, tremors, and dizziness
- Later, complete CNS depression occurs, which culminates in convulsions, apnoea, and coma

Pharmacokinetics

Absorption

It depends on the individual agent, the site of injection (intercostal > caudal > epidural > brachial plexus > SC) and the addition of a vasoconstrictor ± bicarbonate

Less than 10 mg of lidocaine injected in the vertebral/carotid artery can cause coma and convulsions

Distribution

LAs have higher affinity to 1-acid glycoprotein, although albumin binds to more LAs due to its relative abundance

The higher the protein binding, the less available the proportion of the active unbound fraction

Amide LAs are more extensively bound than esters

In certain situations where protein binding is increased, less free drug is available to work, e.g. in renal failure, infants, myocardial infarction (MI), and post-operatively

The higher the protein binding, the lower the degree of placental transfer. There is more placental transfer of lidocaine (70% protein-bound) than of bupivacaine (95% protein-bound)

Esters have rapid metabolism, and therefore, large amounts do not cross the placenta

Metabolism and elimination

Esters are hydrolysed to inactive metabolites by plasma cholinesterases and other esterases. Para-aminobenzoate is one of the inactive metabolites associated with hypersensitivity reactions

Amides are metabolized by amidases in the liver at a rate that is slower than that of plasma hydrolysis; hence, they are more prone to accumulation with continuous infusion

In hepatic ischaemia or in ammation, due to reduced enzyme activity, LA metabolism may be a ected and toxicity can occur

Further reading

1. Peck TE, Hill SA. Local anaesthetics. In: Peck TE, Hill SA (eds). Pharmacology for Anaesthesia and Intensive Care. 4th edition, 2008; pp. 163–74. New York, NY: Cambridge University Press
2. AnaesthesiaUK. https://www.frca.co.uk

6.2 Lidocaine

Class of drug

Amide LA

Indications

Ventricular tachyarrhythmias—class Ib antiarrhythmic activity (level 1 evidence)

Chronic neuropathic pain (level 1 evidence)

Acute neuropathic pain: no level 1 evidence, but widely used based on the evidence for chronic neuropathic pain

Acute perioperative pain (level 1 evidence). A systematic review of 45 randomized controlled trials (RCTs) (2802 post-surgery patients) showed the following:

- Pain scores (numerical rating score) at 1–4 hours reduced by 0.8, at 24 hours reduced by 0.3, and no e ect at 48 hours
- E ective only in open abdominal and laparoscopic surgery
- Trials were heterogenous and small
- Limited evidence of positive e ects on post-operative GI recovery, opioid requirements, post-operative nausea and vomiting, and length of hospital stay

Headaches: migraine, medication overuse headaches (level 1 evidence with variable e cacy)

Contraindications

Known allergy to amide local anaesthetics. Use with caution in patients with myasthenia gravis, severe shock, or impaired cardiac concuction

Preparations

Liquid solutions:

Concentrations: 0.5%, 1%, 2%, 4%, 10%

With or without adrenaline at di erent concentrations

Viscous preparations for mucous membranes (e.g. for urinary catheterization, mouthwashes)

Sprays:

Concentrations: 2%, 4%, 10%

With or without a vasoconstrictor such as phenylephrine

Creams:

Concentrations: 0.5%, 1%, 2%, 4%

Eutectic mixtures such as EMLA™ (2.5% lidocaine and 2.5% prilocaine)

Liposomal lidocaine 4% or 5% (liposomal preparations facilitate the rate and extent of drug absorption and prevent rapid lidocaine metabolism)

Patches:

5% lidocaine (Versatis®): soft, stretchy, adhesive hydrogel plaster, 14 × 10 cm size with 5% lidocaine equivalent to a total of 700 mg. Applied on unbroken, clean, dry skin, and the plasters can be cut to t the painful area being treated. Up to three plasters can be used in each application to cover the area of pain. The plasters are worn 12 hours on and 12 hours o

Lidocaine 7% and tetracaine 7% patch (Synera®, Pliaglis®)

Other preparations: throat lozenges, ointments, eye drops, gel with or without antiseptics such as chlorhexidine

Dosage

Dose varies, depending on the indication (anaesthesia, analgesia for acute/cancer/chronic pain syndromes) and route of delivery:

CNS—intrathecal/epidural

Peripheral nervous system—nerve blocks, local in ltration, catheter infusions, patches

CNS and/or peripheral nervous system—IV infusions

Mucosal surfaces—gel/cream, inhaled, drops, liquid preparations

Doses normally used:

Ventricular tachyarrhythmias: 50–100 mg IV under electrocardiogram (ECG) monitoring at a rate of 25–50 mg/min. Further doses if no response. No more than 200–300 mg over 60 minutes

Anaesthesia without adrenaline 3 mg/kg, and with adrenaline 7 mg/kg

Topical use in awake breoptic intubations—up to 9 mg/kg

Pain management:

Topical use: up to 4 mg/kg

IV/SC use (di erent doses in di erent institutions)

Doses used range from 1–3 mg/kg/hour

In the LOLIPOPS trial (The Long-term Outcomes of Lidocaine Infusions for persistent PostOperative Pain in patients undergoing breast cancer surgery). Dose regime used in the trial (trial has not been published yet):

2.5 mg/kg lean body weight IV as a bolus, after induction of anaesthesia and prior to surgical incision

3.33 mg/kg/hour IV intraoperatively

2.22 mg/kg/hour SC for 24 hours post-surgery

Duration and onset of action

Onset of action: 1–5 minutes

Duration of action: 30 minutes to 2 hours. Addition of adrenaline (concentrations of 1:100 000 or 1:200 000) may extend the duration up to 3 hours

Mode of action

Na^+ channel blockage (see 6.1 Local anaesthetics, p. 101)

At sub-anaesthetic doses, decreased hyperexcitability and spontaneous neural activity

Other postulated mechanisms which can explain its analgesic e ects include:

- Anti-hyperalgesic: increased release of inhibitory NTs (e.g. glycine), less protein phosphorylating pathways (e.g. protein kinase c), and less activity of NMDA receptors and Ca^{2+}-mediated central nociceptive neural excitability
- Stimulation of descending inhibitory pathways by its anticholinergic activity
- Anti-in ammatory: inhibits the release of lysosomal enzymes, activity of granulocytes, and activity of toll-like receptor 4 (a pain-related receptor in glial cells, macrophages, broblasts, T cells, and B cells), resulting in a decreased production of in ammatory cytokines, ILs. Also decreases the activation of phosphorylating cellular pathways, and development of memory of pain (see 2.7 Central sensitization p. 63 & 4.1 Immunology, in ammation, glia and pain p. 79)
- Reduction of transmission of nociceptive signals: monoethylglycinexylidide, a metabolite of lidocaine, increases glycine levels by inhibiting the glycine transporter

5% lidocaine plaster has an additional mechanical action (hydrogel plaster protecting the hypersensitive area)

Side e ects

Similar to other amide LAs

Topical use is sometimes associated with mild sensation of burning, itching, or warmth at the application site

Lidocaine toxicity at >5 mcg/mL serum levels (see 6.8 Local anaesthetic toxicity, p. 116)

Pharmacokinetics

Absorption:

- After topical use, only 3% of lidocaine is systemically available
- Systemic absorption with 5% lidocaine plaster is very low (3%). Plasma concentration with a 3-day application is 130 ng/mL, as compared to 5000 ng/mL required for cardiotoxicity

Distribution: 60–80% protein-bound. A continuous infusion (without a bolus) will take 4–8 hours to achieve a steady-state plasma concentration

Metabolism: N-dealkylation compounds, which are less active than lidocaine and available in low concentrations. Lidocaine has a high hepatic extraction ratio and its metabolism depends not only on hepatic metabolic capacity, but also on hepatic blood ow

Excretion: renal system. Elimination t1/2 is 100 minutes. Context-sensitive t1/2 after a 3-day lidocaine infusion is approximately 20–40 minutes, and there is no accumulation over time in healthy individuals

Pharmacodynamics

CVS: slight increase in peripheral vascular resistance and APs (decreased phase 4 depolarization, conduction velocity, and refractory period). The ED50 (the dose that produces

a speci ed e ect ("response") in 50% of the population under study) of IV lidocaine is 21 mg/kg (95% con dence interval (CI): 19.0–23.4 mg/kg) for ECG evidence of cardiac toxicity
CNS: as other LAs. The ED50 of IV lidocaine for CNS toxicity is approximately 19.5 mg/kg (95% CI: 17.7–21.3 mg/kg)

Special circumstances

Pregnancy: crosses the placental barrier. Despite possible absorption by fetal tissues, no speci c incidence of malformations or other harmful e ects on the fetus have been reported
Breastfeeding: probably excreted in breast milk in very small quantities and generally poses no risk to the child at therapeutic dose levels
Elderly: may require dose reduction

Additional information

Lidocaine is the 'recommended international non-proprietary name', also known as lignocaine

Cost

Lidocaine hydrochloride 0.5% 10 mL (10 ampoules, £7.00)
Lidocaine hydrochloride 1% 10 mL (20 ampoules, £11.21)
Lidocaine hydrochloride 2% 5 mL (10 ampoules, £12.00)
Lidocaine medical plaster 700 mg (30 plasters, £72.40)
Lidocaine ointment 5% (15 g, £6.18)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Cheung HM, Lee SM, MacLeod BA, et al. A comparison of the systemic toxicity of lidocaine versus its quaternary derivative QX-314 in mice. Can J Anaesth 2011;58:443–50
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6.3 Bupivacaine

Presentation and properties

Amide LA
Clear, colourless solution
Concentration 0.1%, 0.25% and 0.5% (with or without adrenaline 1:200 000)
0.5% (heavy) solution with 80 mg/mL glucose (speci c gravity 1.026) for intrathecal use

Indications

Surgical anaesthesia and acute, chronic, and cancer pain responsive to:
Neuraxial block (intrathecal or epidural)

Peripheral major or minor nerve and fascial plane blocks (single shot or infusions)
SC in Itration (single shot or infusions)
Mostly used in acute pain management (perioperatively, labour)

Contraindications

More cardiotoxic than other LAs such as ropivacaine and levobupivacaine
Contraindicated for IV regional anaesthesia

Dose

Maximum dose 2 mg/kg. A 70-kg adult can tolerate well up to 400 mg/24 hours
Can be given topically, intrathecal, epidural, and SC

Mode of action

Block Na^+ channels. The lipid-soluble (unionized) drug permeates through the phospholipid membrane where it is ionized. It then binds to the internal surface of the Na^+ channel and inactivates it
LA dissolves into the phospholipid membrane and may cause swelling and inactivation of Na^+ channels

Side e ects and toxicity

Adverse reactions are rare when there is no overdosage or intravascular administration
CNS: restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, and drowsiness may be early warning signs of CNS toxicity
CVS:

Decreases the slope of the rise in phase 0 of the AP, hence causing direct myocardial depression
Increases the PR and QRS intervals and the refractory period, which can result in cardiac dysrhythmias
Intrathecal/epidural bupivacaine should be used with caution in patients with severe disturbances of cardiac rhythm, shock, heart block, and haemodynamic instability. It is markedly cardiotoxic and can cause myocardial depression
In severe toxicity, there is major CVS and CNS instability (see 6.8 Local anaesthetic toxicity, p. 116)

Pharmacokinetics

Duration of action: long-acting

Dose, route of delivery, vascularity at the injection site, and addition of vasoconstrictors a ect the duration of action
A single epidural injection of 0.5% concentration normally provides a motor block for 2–5 hours. When used at 0.25% or lower concentrations, the duration of action is shorter, with reduced e ects on motor nerves, which can be advantageous post-operatively or during labour
Repeat doses increase the degree of motor block

Absorption: pKa of bupivacaine is 8.1; only 15% is unionized at physiological pH to penetrate phospholipid membranes. Therefore, the onset of action is intermediate- or slow-acting at 10–20 minutes, with peak plasma levels reached within 30–45 minutes
Distribution: very highly protein-bound (95%), hence long duration of action

Metabolism: in the liver by N-dealkylation to pipecolylxylidine and pipecolic acid
Elimination: via urine. Elimination t1/2 160 minutes

Interactions

Increases myocardial depression when given with antiarrhythmics
Risk of cardiac toxicity increases with propranolol

Special circumstances

Safe to use in pregnancy, breastfeeding, paediatric patients, and the elderly

Additional information

When levobupivacaine (S-enantiomer of bupivacaine) is administered via the epidural route, it has a shorter duration of motor blockade and longer sensory blockade, and causes less CVS and/or CNS toxicity than bupivacaine

Cost

Bupivacaine hydrochloride 0.25% 10 mL (20 ampoules, £17.50)
Bupivacaine hydrochloride 0.5% 10 mL (20 ampoules, £18.30)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Peck TE, Hill SA. Local anaesthetics. In: Peck TE, Hill SA (eds). Pharmacology for Anaesthesia and Intensive Care. 4th edition, 2008; pp. 163–74. New York, NY: Cambridge University Press

6.4 Ametop®

Class of drugs

4% tetracaine gel, stored at between 2°C and 8°C

Indications

Dermal anaesthesia (e.g. venepuncture, lumbar puncture, vaccination, and minor super cial surgical procedures such as skin grafting)
Topical skin anaesthesia (e.g. super cial cleaning, debridement of ulcers or burns)

Contraindications

Premature infants or full-term infants under 1 month old
Ester LA allergy
Concomitant use of sulphonamides and/or anticholinesterases
Do not apply on mucous membranes or broken skin

Dose

Available in 1.5 g tubes that delivers 1 g of the drug when squeezed

Apply one tube content in appropriate proportions for venepuncture (30 minutes) and venous cannulation (45 minutes) under occlusive dressing

Children (aged 5 years and above) and adults—maximum ve tubes can be applied at separate sites at a single time

Onset of LA action 30–45 minutes

Duration of action 4–6 hours

Mode of action

(See 6.1 Local anaesthetics, p. 101)

Side e ects

A single application does not generally cause systemic side e ects (S/Es)

Minor S/Es: burning, itching, swelling, or rash at the application site

Pharmacokinetics and pharmacodynamics

Systemic absorption is minimal

Metabolized by enzymatic hydrolysis in blood

Normally causes tetracaine-induced capillary vasodilatation which can help during cannulation

Interactions

As explained in contraindications

Special circumstances

Paediatrics: not recommended in infants under 1 month of age

Pregnancy: can be used

Lactation: not recommended as not known if tetracaine or its metabolites are secreted in breast milk

Cost

Ametop® 4% gel (1 g, £1.08)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Peck TE, Hill SA. Local anaesthetics. In: Peck TE, Hill SA (eds). Pharmacology for Anaesthesia and Intensive Care. 4th edition, 2008; pp. 163–74. New York, NY: Cambridge University Press

6.5 EMLA™

Class of drug

Eutectic mixture of lidocaine 2.5% and prilocaine 2.5% (amide LAs)

Combining lidocaine and prilocaine results in a eutectic mixture which has a lower melting point than its individual components, forming an oil above 16°C

Indications

Dermal anaesthesia (e.g. venepuncture, lumbar puncture, vaccination, and minor super cial surgical procedures such as laceration repair and skin grafting)

Topical skin anaesthesia (e.g. super cial cleaning and debridement of ulcers)

Contraindications

Known sensitivity to prilocaine, lidocaine, or other amide LA

Methaemoglobinaemia: congenital or idiopathic

Glucose-6-phosphate dehydrogenase (G-6-PD) de ciency

Caution if used with class I antiarrhythmic drugs (e.g. tocainide, mexiletine), as toxic e ects are additive and potentially synergistic

Should be avoided on mucous membranes due to its rapid systemic absorption

Dose, onset, and duration of action

Available in 5 g and 30 g tubes

EMLA™ 5% cream contains lidocaine 25 mg/g and prilocaine 25 mg/g

Apply under occlusive dressing

LA onset of action in 30–60 minutes (60 minutes is recommended)

Duration of anaesthesia after removing EMLA™ dressing at least 2 hours

Dose is 1.5–2 g/10 cm^2 for 1–5 hours, maximum dose 60 g, and maximum treatment area 600 cm^2

Children—maximum dose and maximum treatment area:

- 0–3 months: 1 g/24 hours and 10 cm^2
- 3–12 months: 2 g/24 hours and 20 cm^2
- 1–6 years: 10 g/24 hours and 100 cm^2
- 6–12 years: 20 g/24 hours and 200 cm^2

EMLA™ patches 5%:

- One patch covers approximately 10 cm^2 and contains 1 g of EMLA™
- Apply at least 1 hour before procedure
- Children: <3 months old, one patch; 3–12 months, 1–2 patches; and 1–12 years old, up to ve patches

Mode of action

(See 6.1 Local anaesthetics, p. 101)

Side e ects

A single application does not generally cause systemic S/Es

Minor S/Es: burning, itching, swelling, or rash at the application site

Methaemoglobinaemia (<1/1000) has been reported with prolonged use

Pharmacokinetics and pharmacodynamics

Systemic absorption is minimal

Metabolized primarily in the liver

Lidocaine and prilocaine both have rapid onset of action, toxic blood level >5 mcg/mL, and elimination t1/2 100 minutes

Interactions

As explained in contraindications

Special circumstances

Pregnancy: lidocaine and prilocaine cross the placental barrier. Despite possible absorption by fetal tissues, no speci c incidence of malformations or other harmful e ects on the fetus have been reported

Breastfeeding: lidocaine and probably prilocaine are excreted in breast milk in very small quantities and generally pose no risk to the child at therapeutic dose levels

Paediatric: avoid in infants <12 months old at risk of developing methaemoglobinaemia (G-6-PD de ciency, gestational age <37 weeks, and receiving methaemoglobin-inducing drugs such as sulphonamides and phenytoin)

Cost

EMLA™ 5% cream (5 g, £2.25–2.99; 25 g, £11.70; 30 g, £12.30)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Peck TE, Hill SA. Local anaesthetics. In: Peck TE, Hill SA (eds). Pharmacology for Anaesthesia and Intensive Care. 4th edition, 2008; pp. 163–74. New York, NY: Cambridge University Press

6.6 Cocaine

Physiochemical properties and presentations

Ester LA made from *Erythroxylum coca*

Cocaine hydrochloride solution 1–10%

Cocaine paste 1–4%

Mo att's solution (2 mL 8% cocaine, 2 mL 1% sodium bicarbonate, 1 mL 1:1000 adrenaline)

Indications

Local anaesthesia and vasoconstriction of mucous membranes (e.g. oral, laryngeal, and nasal cavities). Vasoconstriction helps in preventing excessive blood loss and reduces obstruction of the operative eld during surgery

Contraindications

Not for oral, SC, IV, neuraxial, or peripheral nerve infusions

Largely metabolized by cholinesterase inhibitors. Therefore, avoid its use in patients with pseudocholinesterase de ciency or those on cholinesterase inhibitors (e.g. echothiopate eye drops for glaucoma, neostigmine for myasthenia gravis) due to the risk of higher blood levels and drug toxicity

Adrenaline increases catecholamine levels and can enhance cocaine toxicity. Thus, avoid sympathomimetic and -modifying drugs such as guanethidine sulphate, reserpine, TCAs, etc.

Epilepsy—lowers the seizure threshold

Can exacerbate porphyria

Dose

Only for topical use on mucosal membranes

Duration of action 20–30 minutes

Maximum total dose 1.5 mg/kg or 100 mg

Toxic dose 3 mg/kg

Aerosol/spray delivery: available in 2.5 mL solution at a concentration of 10% (100 mg/mL). One spray contains 130 microlitres/13 mg of cocaine. Maximum dose for 70-kg adult is equivalent to approximately 8–9 sprays

Mode of action

Inhibits reuptake of serotonin, noradrenaline, and dopamine in the brain, causing cortical stimulation, and may result in restlessness, excitement, euphoria, garrulousness, and increased motor activity

Central sympathetic stimulation

Can exert direct pyrogenic e ect on thermoregulatory centres in the hypothalamus

Blocks Na^+ ions during depolarization, thus blocking initiation and conduction of electrical impulses in nerve cells

Monitoring

Monitoring is always recommended for any signs or symptoms of toxicity

CNS stimulant and used as an illegal recreational drug for its euphoric properties. It is a very frequently used illegal drug

Side e ects and toxicity

Restlessness, excitement, euphoria, increased motor activity, confusion, paranoia, hallucinations, altered tactile sensations, and psychosis

Migraine-like headache may appear as a result of cocaine-induced vascular changes

Reduction of rapid eye movement sleep and total sleep

Anorexic e ect in low doses

Easily crosses the BBB and may lead to breakdown of the barrier

When used above therapeutic doses or in high-risk patients, it can precipitate seizures, hyperpyrexia, pulmonary oedema, gut/myocardial infarction, disseminated intravascular coagulation, rhabdomyolysis, and life-threatening cardiac arrhythmias

Pharmacodynamics

CNS: cortical stimulation, and may result in restlessness, excitement, euphoria, garrulousness, and increased motor activity

CVS: tachycardia and hypertension (causes vasoconstriction). At large doses, can cause ventricular brillation and myocardial depression

Respiratory system: at therapeutic concentrations, increases minute ventilation

Abdominal system: nausea and vomiting

Metabolic: increased body temperature

Pharmacokinetics

Absorption: oral bioavailability 30%, and intranasal bioavailability 50%

Distribution: 98% plasma protein-bound

Metabolism: mostly (90%) by hydrolysis by serum and liver cholinesterases to ecgonine methyl ester, benzoylecgonine, and ecgonine. Also metabolized by oxidation (minor pathway) to produce norcocaine nitroxide, which is responsible for hepatotoxicity when used above recommended doses

Excretion: in urine; 10% excreted unchanged

Interactions

(See in section Contraindications, p. 112)

Special circumstances

Not recommended in paediatric populations, the elderly, pregnancy, and lactation

If used during pregnancy, can cause neonatal dependence

Impairs cognitive function, and can a ect a person's ability to drive safely and operate machinery. Cocaine is on the list of drugs included in regulations under Section 5A of the Road Tra c Act 1988

Cost

Price not found in the British National Formulary (BNF)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Pomara C, Cassano T, D'Errico S, et al. Data available on the extent of cocaine use and dependence: biochemistry, pharmacologic e ects and global burden of disease of cocaine abusers. Curr Med Chem 2012;19(33):5647–57
3. Sharma HS, Muresanu D, Sharma A, Patnaik R. Cocaine-induced breakdown of the blood–brain barrier and neurotoxicity. Int Rev Neurobiol 2009;88:297–334

6.7 Mexiletine

Class of drug and name

Na^+ channel blocker (reduces delay of muscle relaxation/decreases muscle sti ness)

Namuscla®: 167 mg capsules

Indications

Symptomatic myotonia (muscle pain, sti ness, weakness, dysphagia) in non-dystrophic myotonic disorders (only indication in the BNF)

Pain in peripheral neuropathy, refractory pain disorders (successful treatment with IV lidocaine may predict response to mexiletine)

Intractable headache

Cardiac arrhythmias

Contraindications

Heart failure (ejection fraction (EF) <50%), cardiogenic shock

Second- or third-degree atrioventricular (AV) block, sinus node dysfunction

Atrial and ventricular tachyarrhythmias, atrial brillation or utter

Abnormal Q waves, previous MI, angina symptoms

Caution in epilepsy (increased seizure risk)

Severe renal and liver impairment

Dose

Starting with 167 mg/day (for at least 1 week), can be increased to 2 × 167 mg/day (for at least 1 week), then further to 3 × 167 mg/day (maximum daily dose 500 mg, as per the BNF)
If tolerated and needed, careful titration (check serum levels) up to 400–1200 mg/day
Take with food to reduce S/Es

Mode of action

Class Ib antiarrhythmic (oral analogue of lidocaine)
Actions on surface and membranes of skeletal muscle
Blocks neuronal Na^+ channels
May take days or weeks to titrate and to achieve pain relief in chronic pain or myotonia

Monitoring

Obtain baseline ECG (before starting treatment) and when new symptoms occur
Check ECG within 48 hours of starting treatment and during treatment
Check electrolytes before starting and during treatment
Liver enzymes and full blood count (FBC) during therapy (leukopenia is rare)
Check serum mexiletine levels to guide therapy and in cases of S/Es

Side e ects

(Check serum level and ECG. If severe, e.g. arrhythmias, stop drug.)

Stop if new or worsening arrhythmias (AV block)
Common: GI (nausea, vomiting, heartburn, abdominal pain) CVS (arrhythmias, chest discomfort, vasodilation, hypotension), CNS (drowsiness, headache, insomnia, tremor, coordination problems, paraesthesia, malaise, extremity pain, blurred vision, vertigo), skin reactions—more common with serum levels above 2 mcg/mL
Uncommon: seizure, slurred speech
Sedation can happen
Weight gain unusual

Pharmacokinetics

Metabolized in liver by CYP2D6 and 1A2 to less potent metabolite
Half-life: 10–12 hours
Protein binding: 50–60%
Renal impairment: no e ect on dose
Caution in hepatic impairment
Caution in underlying arrhythmias and cardiac failure (possible life-threatening arrhythmias)

Interactions

(Multiple; also check the BNF.)

Ca eine, cimetidine, atropine, opioids, and Mg^{2+} may slow absorption
Metoclopramide increases absorption and levels
CYP2D6 inhibition (propafenone, uoxetine, duloxetine), and CYP1A2 inhibitors (uvoxamine) may increase levels

Pregnancy

Not recommended in pregnancy and breastfeeding (excreted in breast milk)

Additional information

Has been used in the past after successful trial of IV lidocaine

May require individual funding request if used for chronic pain

Cost

Capsule 167 mg: £50 per capsule (£1600–5000 per month)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org

6.8 Local anaesthetic toxicity

Introduction

Maximum LA doses cannot be applied universally, as many factors are important (e.g. body habitus, genetic, gender, pharmacokinetic and pharmacodynamic factors) (see Table 6.8.1)

Bupivacaine appears to be the most toxic LA. Toxic e ects are due to e ects on the excitable plasma membranes of the CNS and CVS

Type of adverse reactions and toxicity to local anaesthetics

Allergic reactions

True allergy is rare

Hypersensitivity to ester LAs is not uncommon. It happens due to para-aminobenzoic acid which is produced when ester LAs are metabolized. It does not cause cross-sensitivity to amides

Additive toxicity

Due to vasopressors and preservatives, e.g. inadvertent vasoconstriction due to cocaine in the presence of other vasoconstricting drugs such as monoamine oxidase inhibitors (MAOIs)

Simultaneous use of other medications which block ion channels (e.g. Na^+, Ca^{2+}, K^+) such as antiarrhythmics, antiepileptics, and antipsychotics

Table 6.8.1 Doses of local anaesthetics

	Lidocaine	Prilocaine	Bupivacaine	Levobupivacaine	Ropivacaine
Maximum dose (without adrenaline)	3 mg/kg	6 mg/kg	2 mg/kg	2.5 mg/kg	3 mg/kg
Maximum dose (with adrenaline)	7 mg/kg	9 mg/kg	2.5 mg/kg	3 mg/kg	4 mg/kg

Local (neuronal) toxicity

Intraneural injection, neuronal ischaemia due to high pressure, and nerve irritation

Methaemoglobinaemia

Iron in haemoglobin (Hb) is altered, reducing oxygen-carrying capacity of Hb. As a result, cyanosis and hypoxia occur

Benzocaine, lidocaine, and prilocaine due to its metabolite O-toluidine cause this e ect

Systemic toxicity

Occurs when plasma concentration reaches beyond toxic levels

Local anaesthetic toxicity—pharmacodynamics

Cardiovascular system

Lidocaine and bupivacaine:

- Block cardiac Na^+ channels, decreasing the slope of the rise of phase 0 of the AP. This leads to direct myocardial depression
- Increased PR and QRS intervals and refractory period (risk of cardiac dysrhythmias)

Bupivacaine has a slow dissociation from cardiac Na^+ channels, hence leading to prolonged myocardial depression and subsequent ventricular dysrhythmias and re-entry arrhythmias

Ropivacaine is a single S-enantiomer of bupivacaine and has a propyl group substitution for the butyl group. This enables its relatively quick dissociation from Na^+ channels; hence, it is less cardiotoxic. Ropivacaine is required in larger doses due to its short duration of action and lower potency than bupivacaine

Central nervous system

LAs penetrate the brain tissue very rapidly and exert a biphasic e ect:

- First phase: inhibit inhibitory interneurons, resulting in an excitatory phenomenon, i.e. perioral twitching/tingling, visual disturbances, tremors, and ts
- Second phase: there is CNS depression, resulting in coma and apnoea

Local anaesthetic toxicity—pharmacokinetics

Absorption

Absorption depends upon speci c character of the agent used, concentration, volume, site of injection, addition of alkaline solutions (e.g. bicarbonate), and vasoconstrictors (e.g. adrenaline)

Risk of toxicity is higher from injection into certain places where the absorption rate is higher than at other sites, i.e. intercostal > caudal > epidural > brachial plexus > SC

Inadvertent intravascular injection can lead to rapid systemic toxicity, e.g. 10 mg of lidocaine injected in the vertebral artery can lead to immediate CNS toxicity

Distribution

1-acid glycoprotein and albumin are the main proteins bound to LAs. Amides (bupivacaine > ropivacaine > lidocaine > prilocaine) are more extensively bound to these proteins than esters. 1-acid glycoprotein binds with greater e cacy; yet albumin, due to its relative abundance, binds more extensively

In conditions where there is increased protein binding (pregnancy, renal failure, post-operatively, and infancy), the free fraction of the LA is reduced, hence less likelihood of toxicity

The degree of protein binding a ects the extent of placental transfer. Bupivacaine, being more bound to protein, crosses the placenta less

Metabolism

Unexpected LA toxicity can occur in cardiac or hepatic failure where drug metabolism is reduced or alterations in plasma protein binding can occur

Treatment of local anaesthetic toxicity

Treatment depends on the severity, following guidelines from the Association of Anaesthetists of Great Britain and Ireland on the management of LA toxicity

Mild toxicity normally presents with a simple rash and improves by stopping further LA injection, giving antihistamines, and observation

In severe toxicity, with CVS and/or CNS instability:

- Stop further LA injection
- Cardiopulmonary resuscitation (CPR), oxygenation, organ support, call for help
- Intralipid® 20% infusion:
  - Mechanism of action is not well understood; seemingly, a pool of lipid in the blood acts as a sink and removes lipophilic LA molecules from cardiac and nervous system tissue reducing neural blockade, seizures and improving cardiac contractility, conduction and coronary blood ow
  - Initial bolus 1.5 mL/kg, and start 15 mL/kg/hour infusion
  - Second bolus 1.5 mL/kg at 5 minutes, and double infusion rate to 30 mL/kg/hour
  - Third bolus 1.5 mL/kg at 10 minutes, and continue infusion
  - Maximum cumulative dose of 12 mL/kg

Critical care support and subsequent monitoring of amylase/lipase for 48 hours

Report/investigate/discuss as per local clinical governance

Further reading

1. Association of Anaesthetists of Great Britain and Ireland. Management of severe local anaesthetic toxicity. 2010. https://anaesthetists.org/Home/Resources-publications/Guidelines/Management-of-severe-local-anaesthetic-toxicity
2. Litz RJ, Popp M, Stehr SN, et al. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia 2006;61(8):800–1
3. Rosenblatt MA, Abel M, Fischer GW, et al. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anaesthesiology 2006;105(1):217–18

CHAPTER 7

Opioids

Enrique Collantes, Praveen Ganty, James Jack, Jonathan Norman, and Jan Rudiger

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7.1 Overview of opioids

Introduction

Opiate use dates from as far back as early Egyptian times, initially as mixed alkaloids from poppies

It was not until the 1970s that opiate receptors and their natural analogues were discovered

All strong opioids are classed as controlled (known as scheduled in the USA) drugs

If opioids are used, doses must be titrated to response (start low and go slow)

Classi cation of opioids

1. Opiates (naturally occurring opioids) = morphine, codeine, and papaverine
2. Semi-synthetic opioids = diamorphine, buprenorphine, and oxycodone
3. Synthetic opioids = fentanyl and its derivatives, methadone, pethidine, tramadol, and tapentadol

Chemical classi cation (four subtypes)

1. Phenanthrenes (morphine, codeine, oxycodone, buprenorphine)
2. Phenylpiperidines (fentanyl derivatives, pethidine)
3. Diphenylheptanes (methadone)
4. Benzomorphans (pentazocine)

Tramadol and tapentadol do not t into this classi cation.

Opioid receptors

(See 3.2 Opioid receptors, p. 72.)

Most opioids used in clinical practice work by binding at the mu opioid (MOP) (or mu) receptors, inducing G-protein-mediated hyperpolarization of the cell

There are several subtypes of the MOP receptor; the di erence is mainly at the external binding site of the receptor, and some of these variants may have an e ect on clinical practice, although this is not fully understood

The other main receptor types are kappa opioid (KOP) (or kappa) and delta opioid (DOP) (or delta) receptors

Mechanism of action

Clinically, opioids act as pure opioid receptor agonists such as morphine, partial agonists (or agonist/antagonist) such as buprenorphine, or agonists at >1 opioid receptor such as oxycodone, codeine, methadone, and pethidine

Some opioids such as tramadol, tapentadol, and methadone also have pharmacological activity at non-opioid receptors (there is some contention as to how useful this is clinically)

The most potent opioid analgesics tend to be pure mu receptor agonists

Metabolism

Metabolism occurs by two pathways:

Glucuronidation (for morphine, hydromorphone, and oxymorphone)

Oxidation (almost all other opioids) via the cytochrome P450 system (for drugs that are oxidized, there is the potential for signi cant drug interactions)

Most opioids produce active metabolites which are clinically relevant

Methadone and fentanyl do not produce clinically relevant active metabolites

Oxycodone, buprenorphine, hydromorphone, and tapentadol produce active metabolites of limited clinical relevance

The pharmacokinetics of opioids varies according to age, sex, and race, and for those opioids metabolized by oxidation by signi cant genetic variability in the cytochrome P450 enzymatic system

Hepatic impairment

Metabolism by glucuronidation and oxidation occurs in the liver. There are multiple changes in the metabolism of opioids in liver impairment. Some of the key changes include:

- Higher oral bioavailability of some opioids because there is less rst-pass metabolism
- Prolonged e ects as opioids are metabolized for clearance more slowly

All opioids need to be used with caution in hepatic impairment. Generally, the doses of opioids and choice of opioids recommended in hepatic impairment include the following:

- No change of dose generally needed: oxycodone, alfentanil, fentanyl, buprenorphine, morphine (reduce dose if morphine being used orally)
- Reduce dose in signi cant hepatic impairment: tramadol, tapentadol, hydromorphone, methadone
- Avoid: pethidine

Renal impairment

Renal impairment has a very important e ect on the doses and choice of opioids selected. Some of the key changes that occur from renal impairment include:

- Decreased excretion of opioids that are excreted by the kidney
- Decreased excretion of active metabolites of opioids
- These patients tend to be on other drugs which are nephrotoxic (e.g. furosemide, angiotensin-converting enzyme inhibitors (ACEIs), gentamicin) and can further worsen the renal function, further limiting the use of most analgesics

All opioids need to be used with caution in renal impairment. Although some have a better pro le, this does not necessarily mean they are completely safe. The choice of opioids recommended include:

- No change of dose needed, as have no active metabolites: fentanyl (rst line), methadone (lower doses in severe impairment)
- No dose changes generally needed, has weakly active metabolites: buprenorphine (excretion of metabolites mostly by biliary metabolism, so the pharmacokinetics of the drug is not majorly a ected)
- No dose changes generally needed in mild to moderate renal impairment, as have low amount of, or weakly active, metabolites: alfentanil, oxycodone, tapentadol
- Ideally another agent should be used, as these have active metabolites: codeine (morphine), tramadol (O-desmethyltramadol), morphine (morphine-6-glucuronide), hydromorphone (hydromorphone-3-glucuronide)
- Contraindicated: pethidine (norpethidine)

Side e ects

(See Table 7.1.1.)

- Wide and similar S/E pro le of opioids between individual drugs
- Reported rate by patients of at least one S/E is 80%, and 50% for two or more

Table 7.1.1 Opioid side e ects according to systems

System	Side e ects
Neurological	Hallucinations, confusion, vertigo, euphoria, dysphoria, mood changes, dizziness, drowsiness, sleep disturbance, headache, miosis, nightmares, visual disturbances, weakness, anxiety, agitation, tremor, brain fog, memory problems, balance problems, mydriasis
Respiratory	Cough, rhinitis, pharyngitis, respiratory depression, dyspnoea, worsening of asthma
Cardiovascular	Bradycardia, tachycardia, palpitations, postural hypotension
Gastrointestinal	Nausea and vomiting, constipation, diarrhoea, stomach pain, atulence, poor appetite
Endocrine	Adrenal insu ciency, dysmenorrhoea, lymphadenopathy, decreased libido (sexual dysfunction), ureteric spasms
Others	Dry mouth, biliary spasm, peripheral oedema, di culty in passing water, urinary retention, ureteric spasm, sweating, ushing, rash, urticaria, itching Serotonin syndrome, rigors, back pain, fatigue (weakness), muscle cramps, sense of body temperature change

Most commonly of **gastrointestinal** origin (including nausea, constipation, and dry mouth) and **neurological** origin (drowsiness, fatigue, poor concentration, and dizziness commonly)

Itching and sweating are also common

Adverse e ects are more common when opioids are used in conjunction with other centrally acting drugs, particularly with benzodiazepines (BZDs)

There is a correlation between serum levels of an opioid and the frequency of S/Es

With chronic use, tolerance may develop to many of the S/Es, with the exceptions of constipation and excess sweating

Opioids have wide-ranging e ects on the **endocrine system**, stimulating the release of insulin and glucagon from the pancreas, as well as growth hormone and prolactin. They inhibit the secretion of adrenocorticotrophic hormone (ACTH) and luteinizing hormone (LH), leading to hypogonadism, decreased libido, impotence, amenorrhoea, and infertility

Opioids appear to have a wide range of possible e ects on the **immune system**, probably with a pro-in ammatory e ect with increased production of TNF- , IL1 and IL6

Opioids have been associated with cases of **serotonin syndrome** either on their own or more often in combination with other serotonergic drugs (tramadol, tapentadol, and methadone are seen as higher risk)

Increasingly, studies looking at **tolerance and hyperalgesia** with opioid use suggest that hyperalgesia tends to occur mostly at higher opioid doses. The mechanisms, while not fully understood, appear to involve both reduced expression and sensitivity of MOP receptors and upregulation of NMDA receptors. The e ects may occur acutely with potent short- acting opioids (e.g. remifentanil), and there is evidence of persistence after cessation of opioid treatment

Contraindications/caution

Patients with, or at risk of, signi cant respiratory depression and/or obstructive airways

Acute intoxication with alcohol, prescribed and not prescribed drugs

Comatose patients, head injury, raised intracranial pressure (ICP)

Severe liver and renal disease

Known allergy or hypersensitivity to opioids

Caution

Children, elderly, pregnancy, drug misuse

Acute abdomen, delayed gastric emptying, heart failure, chronic lung disease, phaeochromocytoma, cardiac arrhythmias, pancreatitis, cor pulmonale, risk of paralytic ileus, acute ulcerative colitis, diarrhoea, antibiotic-associated colitis (e.g. pseudomembranous colitis)

Patients on polypharmacy

Use of opioids for acute pain

Many initiatives and guidelines have been developed to reduce opioid-related harm. It has been recommended to use immediate-release opioids and to avoid slow-release opioids for the management of patients with acute pain, to decrease the risk of respiratory depression

The use of opioid-sparing techniques is recommended (non-steroidal anti-in ammatory drugs (NSAIDs), paracetamol, regional techniques, and other adjuvants)

Long-term use of opioids for chronic non-cancer pain

The bene ts of taking opioids long-term are primarily decreased in pain, although this appears modest at around 20%

Sleep may be improved (worsened in some cases), but there is no convincing evidence that long-term opioids improve function and there is some controversy on how important this is as a primary outcome factor

Evidence for the use of long-acting opioids in chronic non-cancer pain (CNCP) is limited to short-term studies (trials often demonstrate a high rate of dropout due to the lack of e cacy or problems with S/Es)

There is limited evidence demonstrating better outcomes when two or more di erent opioid preparations are used simultaneously

Not all pain is opioid-responsive!

The opioid crisis

The introduction of long-acting formulations in the 1980s led to a rapid rise in the use of opioids for the management of chronic pain from late twentieth century to the present day

During this period, the wish to relieve su ering overcame fears of addiction, which was thought to be as low as 2–3%

More recent studies suggest problem behaviours in at least 10% of patients. It is now clear that long-term use of opioids is also associated with an increased risk of overdose, death, falls, fractures, and accidents, including association with impaired driving, as well as changes to the immune system that may alter response to disease (there is increasing evidence of problem behaviours reported with long-term use, particularly in North America)

There are now guidelines in many countries on how to use and limit strong opioids in chronic pain

These guidelines usually recommend dose limitation (in the UK 120 mg, and in Australia 60–80 mg, of oral morphine equivalent dose per day). This limitation is primarily due to the lack of studies on high-dose opioids, rather than a known lack of e ect

Driving and opioids

The recently updated laws on drugs and driving still allow patients to drive while using opioids in the UK, if they are being used on prescription appropriately and not causing an impairment of judgement

Avoid driving for a few days when commencing a new pain medication (including opioids), increasing or decreasing the dose, or adding another drug (e.g. sedatives) that may a ect driving

In the UK, it is the patient's duty to determine if they are t to drive or not

However, it is against the law to drive if they have been advised not to by a medical professional (May 2020)

Further reading

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7.2 Buprenorphine

Class of drugs

Buprenorphine is a strong opioid, a thebaine derivative (classi ed as a narcotic, controlled drug)

Buprenorphine is an atypical opioid with a di erent mode of action (partial agonist) and a better safety pro le than conventional opioids

Buprenorphine-patch to oral morphine equivalence is 1:60–1:100

Preparations

Sublingual tablets:

- Temgesic®: 200 and 400 mcg; Subutex®: 2 and 8 mg
- Suboxone® (buprenorphine + naloxone in 4:1 ratio): 2 and 8 mg

Oral tablets:

- Espranor® 2 and 8 mg (oral lyophilisate)

Transdermal patches:

- Butrans®, Bunov®, Butec®, Norspan® in doses of 5, 10, 15, 20, 30, 40 mcg/hour
- Bupeaze®, Hapoctasin®, Transtec® in doses of 35, 52.5, 70 mcg/hour

Modi ed-release liquid solution for SC injection (weekly or monthly):

- Buvidal® as 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL, 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL

Liquid solution for IV use:

- Temgesic®: 300 mcg/mL

Indications

Acute pain:

- Sublingual (Temgesic®: 200–400 mcg)
- IM injection of 300–600 mcg (300 mcg/1 mL)

Chronic non-cancer pain (CNCP) and cancer pain (moderate to severe):

- Sublingual (Temgesic®: 200–400 mcg 3–4 times per day)
- Transdermal patches:
  - Butrans®, Butec®, Norspan®: 5–20 mcg/hour every 7 days, assess e ect after 72 hours)
  - Norspan®, Transtec®, Bupeaze®: 35–50–70 mcg/hour every 4 days, assess e ect after 24 hours
- For CNCP, buprenorphine doses should be titrated to a maximum of oral morphine equivalent daily dose (OMEDD) of 80 mg (as recommended by the Faculty of Pain Medicine)

Opioid replacement therapy programme:

Sublingual tablets (Subutex®, Suboxone® = buprenorphine + naloxone), 0.8–4 mg initially, with 4–24 mg/day as maintenance (for opioid substance use and dependence)

Oral tablets (Espranor®)

Modi ed-release SC injection (Buvidal® given weekly or monthly, Sublocade® given monthly)

Premedication (sublingual 400 mcg, IM 300 mcg)

Intraoperative analgesia (slowly IV: 300–450 mcg)

Contraindications

(See opioid contraindications in 7.1 Overview of opioids, p. 119)

Mode of action (partial mu agonist, weak kappa and delta antagonist)

Partial MOP receptor agonist (with high a nity for mu receptors, but low intrinsic activity)

Weak KOP receptor and DOP receptor antagonist

Nociceptin or opioid-receptor-like 1 receptor agonist—most likely explains the speci c advantageous e ects of buprenorphine

As a partial agonist, its maximal opioid e ects are less than e ects of full agonists, and higher doses of buprenorphine can be administered with fewer adverse e ects (e.g. respiratory depression) than seen with higher doses of full mu agonist opioids

At low doses, it is more potent/e cacious than morphine. Opioid-naïve patients can have a very good analgesic e ect when they receive a low dose of buprenorphine (e.g. in rib fractures)

At lower doses, buprenorphine appears to behave as a full agonist, with partial agonist e ect only at higher doses seen in drug dependence programmes

Analgesic e ects reach a ceiling where higher doses of buprenorphine do not result in greater pain relief, but higher doses increase the duration of withdrawal suppression and opioid blockade

Animal studies have shown that when buprenorphine is used with other MOP receptor full agonists (e.g. morphine, oxycodone, fentanyl), buprenorphine displaces and prevents them from acting on the mu receptors, due to high a nity of buprenorphine to mu receptors

This e ect is dose-related, as shown in a study demonstrating that the 16 mg dose of the sublingual buprenorphine-alone tablet was more e ective than the 8 mg dose in blocking the reinforcing e ects of heroin

Therefore, some centres continue buprenorphine in hospitalized patients with acute pain (surgical and non-surgical) and use multimodal analgesia with other MOP receptor agonists

It is di cult for opioid antagonists (e.g. naloxone) to displace buprenorphine and precipitate withdrawal (higher than usual doses of naloxone may be needed in a buprenorphine overdose)

Buprenorphine has a slow dissociation rate from the MOP receptor, which gives rise to its prolonged suppression of opioid withdrawal and blockade of exogenous opioids

This enables buprenorphine dosing to occur on a less frequent basis than full opioid agonists (buprenorphine can be given as infrequently as three times per week)

Monitoring of treatment

Regular liver function tests (LFTs) in patients with hepatic de ciency

Regular clinical supervision as part of a drug maintenance programme

Monitoring of neonates (drowsiness, weight gain, development) recommended in breastfeeding mothers

Androgen de ciency testing is advised only if issues are clinically suspected

Clinical advantages of buprenorphine over conventional opioids (full MOP receptor agonists)

Clinically buprenorphine behaves like a full MOP receptor agonist with similar e cacy and causes fewer adverse e ects

Less respiratory depression with ceiling e ects on respiratory function has been reported at a daily dose of buprenorphine of 16 mg

Can be used in patients with mild-moderate renal failure as there is no build up of active metabolites. In patients with severe renal failure may need to change the doses used

Less opioid-induced androgen dysfunction (due to its partial agonist e ect versus full agonists)

Less opioid-induced hyperalgesia (OIH) due to less activation of glia

Lower rate of sedation and cognitive dysfunction

Less opioid-induced constipation

Long duration of action, enabling dosing to occur on a less frequent basis for the treatment of opioid addiction/dependence, in contrast to other shorter-acting opioids

Other: less itching, safer in the elderly, and milder withdrawal than with other opioids

Clinical disadvantages of buprenorphine over conventional opioids (full MOP receptor agonists)

In overdose, buprenorphine is only partially reversed by naloxone

Buprenorphine can precipitate withdrawal when used acutely in opioid-dependent patients (due to its high a nity and low e cacy at mu receptors). Despite the partial agonist e ect, buprenorphine can cause drug dependence at a lower dose than morphine. Gradual dose reduction is recommended to avoid withdrawal after long-term treatment

When titrating upwards with buprenorphine patches, it is not recommended to increase straight to 35 mcg/hour from 20 mcg/hour. However, some preparations do not allow small dose titrations (Transtec® patches are only available in 35, 52.5, and 70 mcg/hour)

Stigma

Transdermal patches can cause skin erythema (20%)

Pharmacokinetics

Oral bioavailability: poor, only 6% (extensive rst-pass metabolism), making it ine ective when taken orally (Espranor® is a lyophilized (rapidly disintegrating) buprenorphine tablet, which is placed on top of the tongue, with a bioavailability of 25–30%)

Lipid solubility: high (leading to higher bioavailability when administered sublingually)

Protein binding: high (low plasma concentrations, but no obvious correlation between plasma level and clinical e ect)

Vd: >5000 L

Metabolism: hepatic, mainly via dealkylation (CYP450 3A4), but also via glucuronidation (no active metabolites)

Distribution half-life: 2–3 hours (initially)

Elimination half-life: 24–36 hours

Excretion: in urine and faeces

Transdermal patches

The transdermal buprenorphine to oral morphine equianalgesic ratio is about 1:60-1:100 (multiply patch dose in micrograms by 2 to obtain the OMEDD in milligrams), e.g. patch 10 mcg/hour (240 mcg/24 hours) 20 mg of oral morphine/24 hours

Peak plasma levels: 48–80 hours

Time to steady concentration: 72 hours

Half-life after removal of patch: 10–24 hours

Change of patch: every 7 days (5–40 mcg patches)

Suitable for cancer pain and CNCP (not appropriate in acute pain when rapid dose titration is needed)

Sublingual preparations

Forty times more potent than oral morphine (0.4 mg sublingual buprenorphine = 16 mg oral morphine = 5 mg IV morphine)

Bioavailability 50% (due to high lipid solubility)

Peak plasma levels after 90 minutes

Doses for acute pain management in opioid-naïve patients: 0.2–0.6 mg 3–4 times per day (suitable for patients who are nil by mouth)

When used for opioid replacement therapy programmes:

- Doses vary enormously (it can be used in high doses, e.g. 2–32 mg/day)
- Suboxone® contains naloxone to deter the abuse of tablets by crushing and IV injection

Intravenous and intramuscular preparations

Peak plasma levels: IV after 2 minutes and IM after 5 minutes

Dose: 0.3–0.6 mg 3–4 times/day (IV 0.3 mg buprenorphine have produced a greater analgesic e ect than 10 mg IV morphine in double-blind studies in major surgery)

Buprenorphine PCA (demand dose 80 mcg) has been found as e ective as fentanyl PCA in major surgery (this might be useful for acute pain management of patients already on high doses of buprenorphine)

Modi ed-release subcutaneous preparation

Used for the treatment of opioid dependence following stabilization on sublingual buprenorphine/naloxone for >7 days

The available modi ed-release preparations last for 1 and 3 months

To switch from sublingual buprenorphine to the monthly Buvidal® depot preparation:

- Patients on sublingual buprenorphine 8–10 mg/day—can be switched to SC Buvidal® 64 mg/month
- Patients on sublingual buprenorphine 12–16 mg/day—can be switched to SC Buvidal® 96 mg/month
- Patients on sublingual buprenorphine 18–24 mg/day—can be switched to SC Buvidal® 128 mg/month

Interactions

CYP3A4 inhibitors (e.g. azole antifungals, protease inhibitors for HIV) increase the plasma concentrations of buprenorphine and nor-buprenorphine

CYP3A4 inducers (carbamazepine, phenytoin, and rifampicin) have not been investigated but seem likely to reduce the plasma concentrations of buprenorphine

Special circumstances

Not recommended in children under 16 years of age

Unlicensed oral use in children under 6 years

Unlicensed IM and IV use in children under 6 months

In pregnancy, there are insu cient data:

- Neonatal respiratory depression and withdrawal syndrome reported
- There are insu cient data on the safety of naloxone in the fetus (Suboxone® is not used in pregnant women on a buprenorphine maintenance programme)
- Women who are already on Suboxone® and become pregnant normally stop it and rotate to a mono-buprenorphine regime such as Subutex® (this may require more supervision as there is a higher risk of injection abuse of a mono-buprenorphine regime, compared to a Suboxone® regime which contains buprenorphine and naloxone, to decrease the risk of injection abuse)

To be used with caution in sleep apnoea, asthma, simultaneous use of other sedatives/respiratory depressants, and moderate to severe renal and liver impairment

Sublingual tablets

200–400 mcg every 6–8 hours: £0.10–0.20 per tablet (£9–24 per month)

Buprenorphine 2–8 mg tablets sublingual (indicated for management of addiction): £1–3 per tablet (£60–260 per month)

Buprenorphine patches

Lower dose (Butrans® 5–20 mcg/hour): £1.40–14.00 per patch (£5.50–57.00 per month)

Higher dose (Transtec® 35–70 mcg/hour): £2.50–8.00 per patch (£20–63 per month)

Intramuscular or slow intravenous injection

300–600 mcg every 6–8 hours: £0.49–0.98 per injection

Subcutaneous injection

Buvidal® (SC injection) 8–128 mg (£56–240 per month)

Oral lyophilisate

Espranor® 2–8 mg: £6–19 for seven tablets (£25–80 per month)

Cost

(Large variability)

Further reading

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7.3 Codeine

Class of drugs, names

Weak opioid (analgesic, controlled drug)

Codeine phosphate 15 mg, 30 mg, 60 mg

Tablet, oral solution (Galcodine®), as solution for injection

With paracetamol: co-dydramol (8/500), co-codamol (10/500), co-codamol (30/500)

With ibuprofen: Nurofen® Plus (12.8/200)

Indications

Licensed: mild to moderate pain

Unlicensed: diarrhoea, cough suppression

Codeine-speci c contraindications

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Acute ulcerative colitis, antibiotic-associated colitis

All children under 12 years, children under 18 years undergoing removal of the tonsils or adenoids for the treatment of sleep apnoea. Codeine has been implicated in the deaths of children (ultrafast metabolizers produce higher morphine levels, causing respiratory depression). These children normally had other risk factors for respiratory depression

Conditions where abdominal distension develops, conditions where inhibition of peristalsis should be avoided

Known ultra-rapid codeine metabolizers (CYP2D6 variant)—increased risk of respiratory depression, especially if taking other sedatives, sleep apnoea, or other comorbidities that can a ect respiratory function (higher risk of 'euphoria' that can lead to misuse and dependence)

Avoid in renal impairment—accumulation of metabolites of codeine glucuronide and morphine

Caution: acute abdomen, cardiac arrhythmias, gallstones, adolescents aged 12–18 years with breathing problems

Dose

PO/IM 15–60 mg every 4 hours PRN (titrated to e ect), maximum daily dose = 240 mg

Hepatic impairment: may precipitate coma. Avoid or reduce dose

Renal impairment: increased cerebral sensitivity, e ects increased and prolonged. Avoid use or reduce dose

Equivalence and conversion

Oral morphine equivalence 1:8 (oral morphine 30 mg oral codeine 240 mg)

Mode of action

Prodrug converted to the active metabolites codeine 3-glucuronide, codeine 6-glucuronide, norcodeine, and morphine

Principle analgesic e ect (MOP receptor): codeine-6-glucuronide and morphine

Monitoring of treatment

No speci c long-term monitoring required

Codeine—speci c side e ects

(For general opioid side e ects, see 7.1 Overview of opioids, p. 119.)

Abdominal pain and constipation are common

Minimal pain relief in slow CYP2D6 metabolizers (see pharmacokinetics of codeine)

Pharmacodynamics

Respiratory: antitussive. Respiratory depression, ↓ ventilatory response to hypoxia and hypercapnia

Cardiovascular: 10% potency of morphine

GI: constipation secondary to ↓ GI motility

Pharmacokinetics

Oral bioavailability: approximately 90%

Metabolism: hepatic metabolism to 3- and 6-glucuronides of codeine (UGT2B7), norcodeine (CYP3A4), and morphine (CYP2D6)

- 0.5–2.0% of population are ultra-rapid metabolizers: ↑ CYP2D6 activity, very sensitive
- 5–10% poor metabolizers: codeine is ine ective and these patients can experience codeine-related S/Es

Onset of action: 15–30 minutes

Biological half life: 2.5–3 hours

Duration of action: 4–6 hours

Excretion: codeine metabolites excreted renally as conjugates with glucuronic acid

Interactions

Anti-muscarinics: possible increased risk of anti-muscarinic S/Es when given concomitantly

Rifampicin and phenytoin: accelerated metabolism of codeine

Alcohol, antipsychotics: enhanced hypotensive and sedative e ects

Anaesthetic agents: possibly enhance e ects of IV and volatile general anaesthetics

TCAs, sedating antihistamines: sedative e ects possibly increased

Anxiolytics and hypnotics: increased sedative e ects

Cimetidine and some SSRIs: metabolism inhibited

Domperidone: antagonism of domperidone-mediated GI activity

Special circumstances

Pregnancy: neonatal respiratory depression and withdrawal symptoms, and maternal gastric stasis and aspiration pneumonia reported if used peri-partum

Breastfeeding: contraindicated. Secreted into breast milk in small quantities. Higher production of morphine in ultra-rapid metabolizers, with potentially serious respiratory risks to infants from respiratory failure (deaths of newborns have been reported during breastfeeding)

Elderly: possible confusion, oversedation, risk of falls, constipation

Additional information

In acute pain: codeine 60 mg = NNT 7; codeine 60 mg/paracetamol 1 g = NNT 2.2 (paracetamol 1 g with ibuprofen 400 mg = NNT 1.5)

Codeine alone for acute pain has low e cacy. It works better when combined with paracetamol and NSAIDs. Low doses of codeine (8/10/15 mg) used alone are unlikely to produce better analgesic e ect than using paracetamol and NSAIDs

Low-dose over-the-counter codeine preparations, combined with paracetamol and/or NSAID, are easily accessible. Misuse of these preparations commonly lead to patient harm from GI ulceration and bleeding, renal failure (renal tubular acidosis with hypokalaemia), protein-losing enteropathy, and hepatic impairment (toxic paracetamol metabolite)

Studies have shown that low doses of codeine cause neuroimmune changes via the activation of glia, TLRs, and other changes associated with OIH/tolerance. It is hypothesized that this explains higher opioid use after surgery in some patients who were on codeine preoperatively

Cost

Tablets: 15 mg: £0.04/tablet; 30 mg: £0.05/tablet; 60 mg: £0.09/tablet (£ 4.80–10.80 per month, depending on dose)

Syrup: 25 mg/5 mL: £0.05/25 mg

Oral solution: 15 mg/5 mL: £9.90

Injection: 60 mg/mL 1 mL: £2.37

Further reading

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7.4 Dihydrocodeine

Class of drugs, names

Dihydrocodeine tartrate

Semi-synthetic opioid analgesic

DF 118, DHC contus

Indications

Licensed uses: moderate to severe pain, chronic severe pain, antitussive

Unlicensed use: not licensed for children under 4 years

Dihydrocodeine-speci c contraindications

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Acute ulcerative colitis, antibiotic-associated colitis

All children under 12 years, children under 18 years undergoing removal of the tonsils or adenoids for the treatment of sleep apnoea. Codeine has been implicated in children's death (ultrafast metabolizers produce higher morphine levels, causing respiratory depression). These children normally had other risk factors for respiratory depression

Conditions where abdominal distension develops, conditions where inhibition of peristalsis should be avoided

Known ultra-rapid codeine metabolizers (CYP2D6 variant)—increased risk of respiratory depression, especially if also on other sedatives, sleep apnoea, or other comorbidities that can a ect respiratory function (higher risk of 'euphoria' which can lead to misuse and dependence)
Avoid in renal and hepatic impairment
Caution: acute abdomen, cardiac arrhythmias, gallstones, adolescents aged 12–18years with breathing problems

Dose

Moderate to severe pain

PO 30–60 mg 4- to 6-hourly as needed (PRN) (up to 240 mg/day)
SC/IM: up to 50 mg 4- to 6-hourly PRN

Chronic severe pain

PO 60–120 mg 12-hourly (modi ed-release) (max 240 mg/day)

Equivalence and conversion

Oral morphine equivalence 1:8 (oral morphine 30 mg oral codeine 240 mg)

Renal impairment

Avoid or reduce dose; opioid e ects increased and prolonged; increased cerebral sensitivity occurs

Mode of action

The active metabolite dihydromorphine is a highly selective MOP receptor agonist

Monitoring of treatment

No speci c long-term monitoring required

Speci c side e ects

(For general opioid S/Es, see 7.1 Overview of opioids, p. 119.)

Abdominal pain and constipation are common
Minimal pain relief in slow CYP2D6 metabolizers

Pharmacodynamics

Limited data, similar to codeine

Pharmacokinetics

Oral bioavailability: 20%
Distribution: Vd: 1.1 L/kg. Reportedly low protein binding
Metabolism:

Hepatic by cytochrome P450 isozymes CYP 2D6 to active metabolite dihydromorphine and CYP 3A4 to nor-dihydrocodeine. A third primary metabolite is dihydrocodeine-6-glucuronide
Uridine 5 -diphospho-glucurosyltransferase (UGT) enzymes to glucuronidated dihydrocodeine

Onset of action: 30–45 minutes. Peak plasma concentration 1.5–2 hours after oral administration (immediate-release preparation)

Duration of action: immediate release (IR) 4–6 hours
Clearance: 300 mL/min
Elimiation half-life: 240 minutes
Excretion: renal excretion

Interactions

No speci c interactions listed beyond general opioid interactions

Special circumstances

Pregnancy: may cause respiratory depression in the neonate. Codeine, its sister drug, has a possible association with respiratory and cardiac defects in rst trimester
Breastfeeding: avoid

Cost

Tablet

Dihydrocodeine tartrate non-proprietary 30 mg: £0.06/tablet (£7.20–14.40 per month for 30–60 mg four times daily)
Modi ed-release: DHC® Continus® 60 mg: £0.09/tablet

Oral solution

Dihydrocodeine tartrate non-proprietary 2 mg/mL: £7.16/150 mL

Solution for injection

Dihydrocodeine tartrate non-proprietary 50 mg/1 mL: £9.11/ampoule

Further reading

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7.5 Fentanyl

Class of drugs

Strong synthetic opioid
Tertiary amine: synthetic phenylpiperidine derivative

Indications

Acute pain
Palliative care
Sedation/analgesia on intensive care and during procedures

Speci c contraindications/caution

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Speci c: cerebral tumour, diabetes mellitus, impaired consciousness
Buccal use: mucositis
Transdermal use: risk of fatal respiratory depression if used on opiate-naïve patients
IV: respiratory depression persisting post-operatively

Dose

Intravenous

Induction of anaesthesia and supplementation of analgesia: 1–2 mcg/kg
Infusion: 3–4.8 mcg/kg/hour (usually on HDU and ICU)
PCA starting dose of 10–20 mcg every 5 minutes

Epidural

50–100 mcg bolus
2 mcg/mL if mixed with bupivacaine 0.1% or ropivacaine 0.2% infusion

Intrathecal

5–25 mcg bolus

Transdermal patches (12, 25, 50, 100 mcg/hour)

Duration 72 hours. Equilibrium after 12–24 hours
Change patches 72-hourly
Generally avoid in acute and chronic pain

Sublingual/buccal tablet

100, 200, 400, 600 and 800 mcg lozenges/tablets (PRN max. four times daily)

Equivalence and conversion

Transdermal patches (multiply patch dose in micrograms by 3 to obtain the OMEDD in milligrams). For example, a fentanyl patch 25 mcg/hour OMEDD 75 mg
IV fentanyl (conversion factor 200) to calculate to an oral morphine equivalent dose. For example, IV fentanyl 100 mcg oral morphine 20 mg
IV fentanyl 100 mcg IV morphine 7 mg

Mode of action

Highly selective MOP receptor agonist
Activates pre-synaptic Gi-protein receptor, hyperpolarizing the cell membrane by ↑ K^+ conductance
Inhibits adenylyl cyclase: ↓ cyclic adenosine monophosphate (cAMP) production; closure of voltage-gated Ca^{2+} channels also occurs

Monitoring of treatment

Monitor IV use in theatre

Post-anaesthesia care unit (PACU) or level 2 environment in many hospitals (except PCA)

Pharmacodynamics

CNS: 50–80 times analgesic potency of morphine. Little hypnosis and sedation. ↓ minimum alveolar concentration of volatile anaesthetic agents, ↑ e ect of non-depolarizing muscle relaxants. Miosis secondary to Edinger–Westphal nucleus stimulation. Seizure-like motor activity reported—no demonstrable EEG activity

Cardiovascular: bradycardia, cardiovascular response to laryngoscopy and intubation obtunded (cardiac output, mean arterial pressure, peripheral vascular resistance and systemic vascular resistance are stable, and pulmonary capillary wedge pressure is una ected)

Respiratory: potent respiratory depression (↓ respiratory rate (RR) and tidal volumes (T_V)); diminished ventilatory response to hypoxia and hypercarbia. Potent antitussive. Chest wall rigidity reported. Minimal histamine release and bronchospasm

Genitourinary: ↑ tone of ureters, bladder detrusor muscle, and vesicular sphincter

GI: ↓ GI motility, ↓ gastric acid secretion. Sphincter of Oddi spasm and ↑ common bile duct pressure

Miscellaneous: high doses obtund metabolic stress response to surgery. No e ect on ADH and minimal serotonin release

Speci c side e ects

(For general S/Es, see 7.1 Overview of opioids, p. 119.)

Easy to develop tolerance and addiction

Post-operative respiratory depression (secondary peak plasma concentration due to elution from muscle)

Pharmacokinetics

Oral bioavailability: 33%. Transdermal absorption: 47% at 24 hours, 88% at 48 hours, 94% at 72 hours. Drug delivery continues after patch removal

V_D: 0.88–4.1 L/kg; 81–94% protein-bound. No delayed respiratory depression post-intrathecal administration as rapidly absorbed into spinal cord

Metabolism: hepatic metabolism predominantly by cytochrome P450 isozyme CYP 3A4 by N-dealkylation to norfentanyl/subsequent hydroxylation to hydroxypropionyl derivatives. Inactive metabolites and safe to use in renal impairment

Onset of action: 2–5 minutes (IV and sublingual/buccal)

Duration of action: small dose 30–60 minutes, and high dose (>5 mcg/kg) 4–6 hours

Clearance: 13 mL/kg/min

t1/2 elimination: 141–853 minutes (short duration of action of single dose due to redistribution; infusion prolongs duration of action due to saturation of tissues)

Excretion: renal excretion (10% excreted unaltered in urine). Clearance decreased in renal and hepatic impairment

Interactions

Incompatible with thiopentone and methohexital

Special circumstances

Pregnancy: as per morphine
Breastfeeding: monitor infant for opioid-induced S/Es
Not known if removed by haemodialysis

Cost

Sublingual tablet

100 mcg tablet: 10-tablet pack: £49.99 (£150 monthly, depending on dose)

Nasal spray

50 mcg/metred spray; 10-dose pack: £59.50

Solution for injection

Fentanyl citrate 50 mcg/mL, 2 mL ampoule: £0.30; 10 mL ampoule: £0.64

Transdermal patches

12 mcg/hour, pack of 5: £7 (£14–66 monthly, depending on dose)

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7.6 Methadone

Class of drug, names

Strong opioid, controlled drug (methadone hydrochloride)
Tablets: 5 mg
Injection: 10, 20, and 50 mg/mL
Oral solution: 1, 10, and 20 mg/mL

Indications

Methadone (non-proprietary) is primarily used in the treatment of opioid drug addiction
Treatment of severe pain (commonly in palliative care)
Terminal cough (in palliative care)

Speci c contraindications

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Signi cant obstructive airway disease or respiratory depression
Severe hepatic impairment
Ulcerative colitis
MAOIs inhibitors

Mode of action

Methadone is both a potent MOP (mu) receptor agonist, with both high a nity and e cacy (R-enantiomer), and a glutamate (NMDA) receptor antagonist (D-enantiomer)

It is a weak agonist at KOP (kappa) and DOP (delta) receptors

Monitoring

ECG pre-initiation, and on signi cant dose increase in patients at risk of long QT syndrome

Monitoring of hormone levels for all patients on signi cant doses of long-term opioids, and for methadone patients, particularly prolactin

Clinical supervision and urine testing on drug treatment programmes (methadone is present in both saliva and sweat)

Methadone-speci c side e ects

(For general opioid S/Es, see 7.1 Overview of opioids, p. 119.)

Cardiovascular: bradycardia, QT interval prolongation, and torsades de pointes

Respiratory: respiratory depression (immediate/delayed) as has long half-life

Drowsiness is common

Localized pain, erythema, and swelling, with treatment by SC infusion

Stigma

Dose

PO, SC, or IM injection: initially 5–10 mg every 6–8 hours (every 12 hours or once daily if prolonged use)

PO for opioid withdrawal: 10–30 mg once daily, increased by 5–10 mg daily according to response (maximum weekly dose increase: 30 mg), typical maintenance dose 40–120 mg daily

PO for terminal cough (linctus): 1–2 mg every 4–6 hours, reduced to 1–2 mg twice daily if prolonged use

Dose equivalence to oral morphine 1:3–1:20, depending on oral morphine daily dose and the dosing conversion regime used (see Table 7.6.1)

For opioid rotations with methadone, see 7.13 Opioid rotation and conversion, p. 158

Table 7.6.1 Morphine to methadone conversion ratios

Ayonrinde regime		Mercadante regime		Ripamonti regime	
Oral morphine daily dose	Conversion ratio	Oral morphine daily dose	Conversion ratio	Oral morphine daily dose	Conversion ratio
<100 mg	3:1	30–90 mg	4:1	30–90 mg	4:1
101–300 mg	5:1	90–300 mg	8:1	90–300 mg	6:1
301–600 mg	10:1	>300 mg	12:1	>300 mg	8:1
601–800 mg	12:1				
801–1000 mg	15:1				
>1001 mg	20:1				

Pharmacokinetics

Methadone is well absorbed but undergoes signi cant rst-pass metabolism, having a variable oral bioavailability of around 50%

Peak plasma concentration at 4 hours

Methadone is extensively protein-bound and has relatively high lipid solubility

Vd: 100–500 L

The terminal half-life is 12 hours (initially), increasing to 50 hours or more over the rst week of use

The analgesic half-life is often much shorter at 6–8 hours

Methadone undergoes hepatic metabolism primarily via CYP450 3A4 (and CYP450 2D6 to a lesser extent) to inactive metabolites, but a minority is excreted unchanged in the urine (CYP450 3A4 shows signi cant intra-individual variability)

Interactions

CYP450 3A4 and 2D6 inhibitor inducers reduce the plasma concentrations of methadone (examples include carbamazepine, phenytoin, spironolactone, St John's wort, tobacco, alcohol, and rifampicin)

Methadone appears to initially induce its own metabolism

Special circumstances

When used in a drug treatment programme during pregnancy, there is a risk of neonatal opioid withdrawal syndrome; this ideally needs to be anticipated and managed in a hospital setting. Methadone should not be used in labour. It is excreted in breast milk

Methadone is not suitable for children

Use with caution in the elderly as clearance is reduced

Clearance is higher in females than in males

Additional information

Methadone slowly accumulates after initiation, lengthening the half-life and leading to an increased risk of overdose (caution needed when switching from other opioids to methadone)

Due to its dual e ect, methadone might have an advantage in treating chronic neuropathic pain over other opioids (in practice, there has been an increase in mortality associated with its use)

When used in opioid withdrawal programmes, patients may attempt to trick urine testing by adding methadone directly to their urine (while methadone is excreted directly in the urine, so is its major metabolite 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine perchlorate, meaning this is easily spotted)

Methadone may be associated with a lower rate of tolerance, dependence, and withdrawal. Tolerance may be rapidly lost on discontinuation

Cost

Methadone 5 mg tablets: £0.05 per 50 tablets (£12–36 per month)

Methadone 1 mg/mL solution: £1 per 100 mL

Methadone 10 mg/mL solution: £12 for 150 mL

Methadone 50 mg/mL for injection, 1 mL ampoule: £1.50 (£45–90 per month)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Electronic Medicines Compendium (emc). Methadone 5mg hydrochloride tablets. 2020. https://www.medicines.org.uk/emc/product/3568/smpc
3. Ostgathe C, Voltz R, Van Aaken A, et al. Practicability, safety, and e cacy of a 'German model' for opioid conversion to oral levo-methadone. Support Care Cancer 2012;20:2105–10
4. US Food and Drug Administration. Methadone. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/006134s045lbl.pdf

7.7 Morphine

Class of drugs, names

Phenanthrene derivative (morphine hydrochloride or morphine sulphate)
Strong opioid (analgesic, controlled drug)

Indications

Licensed uses

Acute pain
Chronic pain
Pain management in palliative care
Cough in terminal disease
Premedication
PCA
Myocardial infarction (MI)
Acute pulmonary oedema
Dyspnoea at rest in palliative care

Unlicensed uses

Morphine sulfate solution PO in children aged under 1 year
Sevredol® tablets in children aged under 3 years
Suppositories not licensed for rectal use in children

Speci c contraindications

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Hepatic impairment

Use with caution, can precipitate encephalopathy
Reduce dose (avoid oral preparations in acute impairment)

Renal impairment

Avoid use or reduce dose (active metabolite morphine-6-glucuronide accumulates)
Opioid e ects potentiated and prolonged with increased cerebral sensitivity

Dose

Oral

Initially 10 mg 3- to 4-hourly, titrate to response

Elderly: 2.5–5 mg 4-hourly

Intravenous, subcutaneous, or intramuscular

0.05–0.1 mg/kg 3- to 4-hourly. Doses normally used in opioid-naïve patients: 5–10 mg, titrated to response (dose can be adjusted more frequently during titration). Decreased dose in frail and elderly patients

Intrathecal (100–200 mcg) or epidural (1–2 mg)—preservative-free

(See 20.8 Intrathecal drug delivery systems, p. 384)

Rectal

Initially 15–30 mg every 4 hours

Mode of action

Agonist at mu and kappa receptors

Increases intracellular Ca^{2+} concentration, increasing K^+ conductance and hyperpolarization of excitable cell membranes

Decreased membrane excitability decreases pre- and post-synaptic responses

Monitoring of treatment

Ward-based monitoring in quoted doses (sedation scores, HR, oxygen saturation (SpO_2), RR, BP)

Closer monitoring if higher doses, e.g. in post-anaesthetic care unit

Monitor kidney and liver function regularly (in acute post-operative pain, every 2–3 days)

Speci c side e ects

For general S/Es, see 7.1 Overview of opioids, p. 119

Pharmacodynamics

CVS: minimal. Orthostatic hypotension, bradycardia

RS: respiratory depression with decreased ventilatory response to hypoxia and hypercarbia. Antitussive. Bronchoconstriction at high doses

CNS: drowsiness, relief of anxiety, euphoria, miosis, seizure activity at high doses

GI: constipation. Decreases gastric, biliary, and pancreatic secretions. Sphincter of Oddi spasm

GU: urinary retention

Other: histamine release, pruritus

Pharmacokinetics

Oral bioavailability: 15–50% (commonly regarded to be 30%). Well absorbed, but extensive rst-pass metabolism

Distribution: 20–40% protein-bound in plasma, predominantly to albumin. Vd 3.4–4.7 L/kg (slow equilibration between plasma and CSF; no clear correlation with degree of analgesia and plasma concentration)

Metabolism: hepatic to morphine-3-glucuronide (arousal), morphine-6-glucuronide (analgesia) and normorphine
Onset of action: 30–60 minutes
Duration of action: 3–4 hours
Biological half-life: 2.5–3 hours
Clearance: 12–23 mL/min/kg
half-life elimination: 1.7–4.5 hours
Excretion: predominantly renal as glucuronide conjugates; 10% excreted in faeces as conjugated morphine

Interactions

Alcohol and antipsychotics: enhance hypotensive and sedative e ects when co-administered
MAOIs: possible CNS excitation or depression with co-administration and up to 2 weeks after cessation
Moclobemide: possible CNS excitation or depression
Gabapentin: morphine increases bioavailability
Esmolol: morphine possibly increases its plasma concentration
Domperidone and metoclopramide: opioid analgesics antagonize e ects on GI activity
Baclofen and sedative antihistamines: increased sedative e ect when co-administered with morphine
Sodium oxybate: opioids enhance e ects; avoid concomitant use

Special circumstances

Pregnancy: neonatal respiratory depression and withdrawal symptoms, and maternal gastric stasis and aspiration pneumonia reported if used peri-partum
Breastfeeding: therapeutic doses unlikely to a ect infant
Elderly: possible confusion and oversedation

Additional information

Can precipitate dependence, tolerance, and addiction, as with other opioids
Decrease dose gradually to avoid withdrawal and abstinence symptoms, especially if taken for longer periods
Available in combination with cyclizine (for short-term use in moderate to severe pain)
Not removed by haemodialysis or peritoneal dialysis

Cost

Immediate-release morphine

Morphine tablets—Sevredol® 10 mg: £0.10/tablet (for 20–40 mg/day: £6–12 per month)

Modi ed-release morphine

Capsules—Zomorph® 10 mg: £0.06/capsule (10 mg twice daily: £3.50 per month)
MST®—tablets 10 mg: £0.06–0.09/tablet (10 mg twice daily: £4–5 per month)
MST Continus® suspension (granules) 20 mg: £1.22/sachet (20 mg twice daily: £73 per month)

Oral liquid solutions

Non-proprietary 10 mg/5 mL: £1.68/100 mL (for 20–40 mg/day: £5–10 per month)
Oramorph® 10 mg/5 mL: £1.89/100 mL (for 20–40 mg/day: £5.70–11.40 per month)

Solution for injection

10 mg/1 mL: £1.10/ampoule

For IV infusion—50 mg/50 mL: £5.78; 100 mg/50 mL: £6.48

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Scarth E, Smith S. Drugs in Anaesthesia and Intensive Care. 5th edition, 2016. Oxford: Oxford University Press

7.8 Naloxone

Class of drugs, names

Naloxone hydrochloride substituted oxymorphone derivative

Opioid receptor antagonist (mu > delta > kappa > sigma)

Indications

Licensed use: overdose with opioids in medical or non-medical setting

Reversal of post-operative respiratory depression

Treatment of clonidine overdose

Caution

Cardiovascular disease (those receiving cardiotoxic drugs)

Pregnancy—maternal opioid dependence (precipitation of opioid withdrawal in newborns)

Patients with opioid dependence—sudden cessation of opioids causes are-up of pain and opioid withdrawal symptoms

Titration of dose—titrate dose for each patient to obtain su cient respiratory response without completely antagonizing the analgesic e ects of opioids

Dose in opioid overdose (intravenous)

>12 years: initially 400 mcg, then 800 mcg up to two doses at 1-minute intervals. Increased to 2 mg for one dose if still no response; 4 mg may be required in severe poisoning. Then review diagnosis

Child aged 1 month to 11 years: initially 100 mcg/kg; if no response, repeat at 1-minute intervals to maximum of 2 mg, then review diagnosis

Adequate IV dose is that which maintains satisfactory ventilation for at least 15 minutes

Continuous infusion (all ages): start rate at 60% of initial resuscitative dose per hour. Titrate to response for all ages

Dose for reversal of post-operative respiratory depression (intravenous)

>12 years: 100–200 mcg or bolus 1.5–3 mcg/kg. If adequate response, give subsequent doses of 100 mcg every 2 minutes or 100 mcg IM every 1–2 hours

Mode of action

Competitive antagonist at MOP, DOP, KOP, and sigma opioid receptors
Negligible a nity to nociceptin opioid peptide (NOP) receptors
Reversal of MOP receptor e ects: sedation, respiratory depression, dysphoria

Monitoring of treatment

Close monitoring of vital signs (sedation scores, HR, BP, RR, SpO_2) in context of opioid overdose

Side e ects

In presence of opioids: sweating, nausea, restlessness, trembling, vomiting, ushing, and headache
Rarely arrhythmia, seizures, and pulmonary oedema
Serious ventricular dysrhythmias in patients with irritable myocardium

Pharmacodynamics

GI: reverses opioid-induced spasm of sphincter of Oddi
CNS: slight drowsiness at high doses. Obtunds some forms of stress-induced analgesia. Decreases pain tolerance in those with high pain thresholds
Cardiovascular: no e ect at normal doses. Increased BP with doses >0.3 mg/kg

Pharmacokinetics

Oral bioavailability: 2% oral bioavailability (91% absorbed, but extensive rst-pass metabolism)
Vd: 2 L/kg, 46% protein-bound
Metabolism: hepatic metabolism by conjugation to glucuronide
Onset of action: IV, 2 minutes; IM, 5 minutes
Duration of action: approximately 20 minutes
Clearance: 25 mL/min
Plasma half-life: 1.2 hours
Excretion: renal excretion

Special circumstances

Pregnancy: no adverse e ects known, but use only if potential bene t outweighs risk (animal studies do not suggest detrimental e ects)
Neonates/infants: can be used in the presence of respiratory depression if the mother has been exposed to opioids during the pregnancy

Additional information

Alleviates pruritus, nausea, and respiratory depression associated with epidural or intrathecal opioids (in small IV boluses of 25–50 mcg)
Available in combination with buprenorphine (Suboxone®) as an adjunct in the treatment of opioid dependence
Available in combination with oxycodone (Targinact®) for pain management (associated with less opioid-induced constipation)
Rarely used for severe idiopathic restless legs syndrome after failure of dopaminergic therapy (no good evidence to support this indication)

Naloxone (IV 0.5 mg/kg) sometimes used for opioid-induced urinary retention, with minimal worsening of pain severity. This can be found sometimes in children receiving opioids for acute pain management

Cost—injection (non-proprietary)

20 mcg/mL, 2 mL ampoule: £5.50
400 mcg/mL, 1 mL ampoule: £3.60–4.50
1 mg/mL, 2 mL pre lled syringe: £16.80

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Scarth E, Smith S. Drugs in Anaesthesia and Intensive Care. 5th edition, 2016. Oxford: Oxford University Press

7.9 Naltrexone

Class of drugs, names

Opioid receptor antagonist (competitive)
Adepend®, Naltrexone®, Nalorex®, Naltrexone hydrochloride

Indications

Prevention of relapse in previously opioid- or alcohol-dependent patients (to be initiated under specialist supervision, unlicensed for alcohol-dependent patients)
Naltrexone has also been combined with opioids (morphine, oxycodone), and there is some evidence of reduction in tolerance, possibly enhanced analgesia, and reduced abuse potential
Methylnaltrexone is a peripherally acting MOP receptor antagonist that is licensed as SC injection in the treatment of opioid-induced constipation
Naltrexone with bupropion (Mysimba®) is licensed for weight loss in obesity, in conjunction with dietary measures and increased physical activity (especially if patients have cardiac risk factors such as diabetes, hypertension, and dyslipidaemia)

Contraindications

Avoid in acute hepatitis and severe hepatic and/or renal failure
In patients who fail a naloxone challenge test (where an injection of naloxone elicits acute e ects of opioid withdrawal)
In patients not opioid-free for 7 days pretreatment
Uncontrolled hypertension, epilepsy, CNS tumour, bipolar disorder, bulimia, anorexia nervosa
Patients undergoing acute opioid, alcohol, or BZD withdrawal
Use of MAOIs with last 14 days

Mode of action

Naltrexone is a competitive antagonist acting at all three classic opioid receptors (MOP, DOP, KOP), possessing high a nity for the receptors, but no e cacy

Monitoring

LFTs before and during treatment

Signs of opioid withdrawal if used in patients on long-term opioids

Side e ects

GI: nausea, vomiting, loss of appetite, thirst, diarrhoea, abdominal pain. The most common reason for discontinuation of naltrexone in trials was nausea

CNS: headaches, fatigue, irritability, mood swings, sleep disruption

General e ects: muscle pain, sweating, impotence, and delayed ejaculation are also common

Dose

Oral

Opioid/alcohol dependency

Naltrexone hydrochloride initiated at 25 mg once daily

Standard dose: 50 mg once daily

Once established, it can also be used at 100–150 mg once every 2–3 days (maximum weekly dose 350 mg)

Weight management

Mysimba® 8/90 (naltrexone hydrochloride 8mg/bupropion hydrochloride 90mg)

Initiate once daily

Increase by one tablet every week. Maximum four tablets daily

Subcutaneous (opioid-induced constipation)

Methylnaltrexone 8 mg (38–61 kg) and 12 mg (62–114 kg) used on alternate days normally

Intramuscular (alcohol dependence)

Vivitrol® 380 mg injection every 4 weeks

Pharmacokinetics

Oral bioavailability: only 25% (oral dose well absorbed, but extensive rst-pass hepatic metabolism)

Peak plasma levels: within 1 hour

Vd: 1300 L, 20% protein-bound

Metabolism:

- Predominantly reduction (independent of the cytochrome P450 system)
- Metabolites are clinically inactive. Mainly renally excreted
- Elimination half-life: 4–12 hours

Interactions

Should not be used in conjunction with opioid medication

Caution with any medications that may cause sedation, especially thioridazine

Special circumstances

Not recommended in children and breastfeeding mothers (due to potential toxicity)

Pregnancy: naltrexone has been reported to be toxic in animal studies (use only if bene t outweighs risk)

Elderly: not recommended in patients aged >75 years, and avoid in patients aged >65 years

Additional information

Reported as useful in cholestatic pruritus

Naltrexone does not appear to increase or decrease suicide risk in patients

Hepatotoxic in overdose, though data are limited—but appears non-toxic at a dose of 800 mg/day (very high doses of opioids are needed to re-narcotize a patient on naltrexone, which leads to a large histamine release)

Naltrexone produces pupillary constriction; the mechanism is unknown

Tolerance is not an issue with prolonged use

Cost

Naltrexone 50 mg: £0.80–1.80 per tablet (£25–55 per month)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Electronic Medicines Compendium (emc). Naltrexone Hydrochloride 50mg Imcoated tablets. 2014. https://www.medicines.org.uk/emc/product/6073/smpc#gref
3. National Institute for Health and Care Excellence (NICE). Naltrexone for the management of opioid dependence. TA115. 2007. https://www.nice.org.uk/guidance/ta115
4. US Food and Drug Administration. Vivitrol (Naltrexone). 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf

7.10 Oxycodone

Class of drugs, names

Semi-synthetic opioid (oxycodone hydrochloride)

Abtard®, Carexil®, Longtec®, Oxeltra®, OxyContin®, Oxylan®, Reltebon®, Zomestine® (slow release)

Capsules: Lynlor®, OxyNorm®, Shortec® (immediate release (IR))

Oral solution/solution for injection: oxycodone, OxyNorm® (IR)

Indications (licensed)

Moderate to severe post-operative/palliative care pain

Speci c contraindications/caution

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Hepatic impairment

Initial dose reduction of 50% in mild impairment (e.g. maximum initial dose 2.5 mg 6-hourly in opioid-naïve patients), adjust according to response

Avoid in moderate to severe impairment

Renal impairment

Maximum initial dose 2.5 mg 6-hourly in opioid-naïve patients with mild to moderate impairment

Avoid when eGFR <10 mL/min/1.73 m^2

Dose

Oral (uptitrate as required)

Immediate release: initially 5 mg 4- to 6-hourly

Modi ed release (MR): initially 10 mg 12-hourly

Intravenous

Bolus: 1–10 mg 4-hourly PRN by slow IV injection

Infusion: initially 1–2 mg/hour, titrate to response

PCA: typically 1 mg/5 minutes

Subcutaneous

Bolus: initially 5 mg 4-hourly PRN

Infusion: initially 7.5 mg every 24 hours, titrate to response

Equivalence and conversion

Oral oxycodone 3 mg IV oxycodone 1 mg

Oral morphine equivalence 1.5:1 (oral morphine 15 mg oral oxycodone 10 mg)

Mode of action

Agonist at MOP, KOP, and DOP receptors

↑ intracellular Ca^{2+} concentration, ↑ K^+ conductance, and hyperpolarization of excitable cell membranes

Inhibition of adenylyl cyclase: ↓ cAMP production, causing closure of voltage-sensitive Ca^{2+} channels. ↓ membrane excitability, decreasing pre- and post-synaptic responses

Monitoring of treatment

Close monitoring in context of opioid overdose and tolerance, dependence, and diversion

Speci c side e ects

(For opioid S/Es, see 7.1 Overview of opioids, p. 119)

Pharmacodynamics

Cardiovascular: minimal orthostatic hypotension

Respiratory: respiratory depression with decreased ventilatory response to hypoxia and hypercarbia. Antitussive. Bronchoconstriction at high doses

CNS: drowsiness, relief of anxiety, euphoria, miosis, seizure activity at high doses

GI: constipation

Genitourinary: urinary retention

Other: histamine release, pruritus

Pharmacokinetics

Oral bioavailability: 60–87%

Vd: 2.6 L/kg; 45% protein-bound

Metabolism: hepatic metabolism, CYP450 3A to noroxycodone, CYP450 2D6 to oxymorphone and other conjugated glucuronides

Onset of action: PO IR: P_{max} 1–1.5 hours; PO MR: P_{max} 3 hours

Duration of action: PO IR: 3–6 hours. PR 6–10 hours

Clearance: 800 mL/min

Elmination half-life: IR 3 hours; MR 4.5 hours

Excretion: 19% free drug, 50% conjugated oxycodone, and 14% conjugated oxymorphone excreted in the urine

Interactions

Alcohol: enhances hypotensive and sedative e ects

Buprenorphine: possible opioid withdrawal

Telithromycin: inhibits oxycodone metabolism

Itraconazole, ketoconazole, voriconazole: increases plasma concentration of oxycodone

Domperidone and metoclopramide: opioid analgesics antagonize the e ects on GI activity

Special circumstances

Pregnancy: penetrates the placenta

Breastfeeding: avoid (present in milk)

Elderly: reduce dose

Additional information

Reduce dose gradually after long-term treatment to avoid withdrawal symptoms

Not removed by haemodialysis or peritoneal dialysis

Cost

MR tablet (slow release)

Abtard®, Carexil®, Longtec®, Oxeltra®, OxyContin®, Reltebon® 10 mg: £0.11–0.45/tablet (£6.70–27.00 per month)

Capsule (immediate release)

Lynlor®, OxyNorm®, Shortec® 10 mg: £0.25–0.41/capsule (at 20–60 mg per day = £13.70–75.00 per month)

Oral solution (immediate release)

Non-proprietary, OxyNorm® 1 mg/mL: £3.84/100 mL (10 mg = £0.38) (at 20–60 mg per day = £2.30–68.00 per month)

Solution for injection

Non-proprietary, OxyNorm® 10 mg/1 mL: £1.60/ampoule

Non-proprietary, OxyNorm® 50 mg/1 mL: £14.02/ampoule

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Scarth E, Smith S. Drugs in Anaesthesia and Intensive Care. 5th edition, 2016. Oxford: Oxford University Press

7.11 Tapentadol

Class of drugs, names

Strong opioid (controlled drug) (tapentadol hydrochloride)

Tapentadol hydrochloride (oral solution 20 mg/mL, MR tablets 50–250 mg, IR tablets 50–75 mg)

Indications

Licensed for moderate to severe pain in acute pain in adults

Sustained-release formulation for severe chronic pain only

Contraindications (tapentadol-speci c)

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Known hypersensitivity/allergy to tapentadol

Paralytic ileus

Recent use of MAOIs (within 14 days)

Acute intoxication with another centrally acting drug

Avoid in severe hepatic impairment and severe renal impairment, epilepsy, seizure susceptibility, and impaired consciousness

Mode of action

MOP receptor agonist

Inhibition of noradrenaline uptake

Therefore, e ective at ascending and descending pain pathways

Monitoring

Pain score, sedation score, and RR

LFTs recommended for patients with hepatic impairment

Testing for androgen de ciency (advised only if clinically suspected)

All patients treated with stronger opioids should be monitored for evidence of misuse

Tapentadol-speci c side e ects

(For general opioid S/Es, see 7.1 Overview of opioids, p. 119.)

Less respiratory depression, nausea, vomiting, pruritus, and constipation than with other opioids which are full MOP receptor agonists (e.g. oxycodone)

Headaches, seizures (rarely)

Associated with serotonin syndrome (rarely), which may be precipitated if administered with medications that increase serotonin levels such as triptans, TCAs, SSRIs, and SNRIs

Dose

Modi ed-release

Starting dose: 50–100 mg every 12 hours (start with 50 mg in opioid-naïve patients)

After initiation, the dose should be titrated individually to provide adequate analgesia and avoid S/Es (including pain severity, previous treatments, and adjusted according to response)

Increments of tapentadol 50 mg twice daily every 2–3 days have been shown to be appropriate to achieve adequate analgesia

Maximum daily dose: 500 mg

Immediate-release

50–100 mg every 4–6 hours

Maximum daily dose: 600 mg (700 mg in rst 24 hours)

Other points on dose ranges

Tapentadol MR can be combined with tapentadol IR for breakthrough pain

The e ective steady-state dose of tapentadol has been shown to be between 300 mg and 350 mg per day

Other guidelines recommend a daily maximum dose of 250 mg tapentadol (= 80 mg oral morphine equivalent dose)

When switching from other opioids to tapentadol, a higher initial dose of tapentadol may be required (see Table 7.11.1)

Abrupt discontinuation of tapentadol may cause withdrawal symptoms (therefore, taper the dose gradually)

Reduced doses are recommended in patients aged over 65 years and in moderate renal and hepatic impairment

Equivalence to other opioids

Equianalgesic doses are based on expert opinions (limited data)

For opioid conversions, the usual equipotent dose reduction of 25–50% is recommended

The relative potency of tapentadol to oxycodone is estimated to be 1:5 (oral oxycodone MR 10 mg = oral tapentadol 50 mg)

Morphine equivalence has also been quoted as 3:10 (oral morphine 15 mg = oral tapentadol 50 mg)

Table 7.11.1 Opioid conversion to tapentadol

Current opioid	Current opioid dose			
Hydromorphone, oral (mg/day)	11	12–15	16–19	20–27
Oxycodone, oral (mg/day)	39	50–59	60–79	80–99
Morphine, oral (mg/day)	79	80–119	120–159	160–199
Buprenorphine patches (mcg/hour)	34	35–52.4	52.5–69	70–87.4
Fentanyl patches (mcg/hour)	37	37.5–49.9	50–74	75–86
Starting dose of tapentadol (slow release)	50 mg × 2/day	100 mg × 2/day	150 mg × 2/day	200 mg × 2/day

Modi ed from Sanchez del Aguila et al., 2015 and with permission from Grunenthal Ltd.

Opioid conversion to tapentadol

The gures provided are an approximate guide to a range of doses of other opioids to one dose of tapentadol MR.

Pharmacokinetics

Oral bioavailability: about 30% due to rst-pass metabolism (despite initial high oral absorption)

Peak plasma level: 80 minutes

Vd: 500–1200 L, 20% protein-bound

Metabolism:

97% metabolized by conjugation with glucuronic acid (high metabolic rate implies extra-hepatic metabolism)

A minority part of metabolism is via the cytochrome P450 system

The metabolites are clinically inactive, and 99% excreted by the kidney

Terminal half-life: 4 hours

Interactions

Direct interactions appear minimal as tapentadol metabolism is through a high capacity system that is not easily saturated

Further, tapentadol is neither highly protein-bound (20%) nor does it appear to interfere with the cytochrome P450 system

Tapentadol should not be used with other opioids, and caution with other drugs with possible centrally acting depressant e ects

Medicines and Healthcare products Regulatory Agency (MHRA)/Commission on Human Medicines (CHM) advice (BNF)

Prescribe with caution in patients with a history of seizures and epilepsy (can lower seizure threshold, in particular if prescribed with antidepressants, e.g. SSRIs, SNRIs, TCAs, antipsychotics)

Serotonin syndrome has been reported in combination with serotonergic antidepressants (SSRIs, SNRIs, TCAs)

Withdrawal of the serotonergic substance usually improves serotonin syndrome rapidly

Special circumstances

Not licensed for use in children

However, the oral solution can be used from the age of 2 at a dose of 1.25 mg/kg every 4 hours; do not exceed the calculated dose for a bodyweight on the 97.5th percentile for the given age, with a maximum of 100 mg per dose) (see BNF for Children)

High serum levels occur in patients with signi cant hepatic impairment

Avoid in pregnancy (no information available, risk of respiratory depression and withdrawal in neonates)

Excreted in breast milk. Avoid with breastfeeding (no information available)

Additional information

Pharmacokinetics are similar in the elderly and in renal failure, although metabolites may accumulate with signi cant renal failure

Tapentadol has reduced abuse potential, compared to opioids, which are full MOP receptor agonists

Tapentadol has signi cantly less a nity to opioid receptors than morphine (1/10 to 1/18 weaker than the binding a nity of morphine to mu receptors) but is an equipotent analgesic, suggesting that its actions on noradrenaline reuptake are relevant to the analgesic e ect. Its action on opioid receptors account for approximately 30% of its activity, and its action on noradrenaline reuptake accounts for 70% of its activity

Less activity on opioid receptors and most of its activity on noradrenaline reuptake is a hypothesis to explain a better S/E pro le associated with tapentadol. Studies have reported a lower risk of respiratory depression, less tolerance and constipation/nausea/vomiting, and less immunosuppression with tapentadol versus conventional opioids (full MOP agonists)

Use with caution in patients on centrally acting drugs for Parkinson's disease, and those with dystonia, dementia, or psychiatric conditions (especially elderly patients)

Advantages of tapentadol versus tramadol: less risk of developing seizures, less confusion or cognitive dysfunction, less risk of serotonergic reactions, safer in mild/moderate renal impairment, less interactions with TCA, SSRIs, and SNRIs, minimal CYP450 metabolism

Disadvantages of tapentadol versus tramadol: no IV preparation, more expensive; currently, there is less evidence on tapentadol in pain management because it is a newer drug

Cost

Tapentadol IR oral solution (20 mg/mL): £0.45–0.90 for 50–100 mg (£18 per 100 mL bottle)

Tapentadol IR tablets 50–75 mg (£0.45–0.67/tablet) (£13.50–81.00 per month)

Tapentadol MR tablets 50–250 mg (£0.45–2.25/tablet) (£27–133 per month)

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7.12 Tramadol

Class of drugs, names

Moderately strong opioid (tramadol hydrochloride)

Racemic synthetic aminocyclohexanol opioid

Indications

Licensed uses: moderate to severe acute/chronic/post-operative pain

Unlicensed use: intraoperative use—may enhance awareness with light anaesthesia; treatment of post-operative shivering

Tramadol-speci c contraindications

(For general opioid contraindications, see 7.1 Overview of opioids, p. 119.)

Uncontrolled epilepsy
Avoid in severe hepatic and renal impairment, pregnancy, and breastfeeding
History of epilepsy, seizure susceptibility, impaired consciousness
Use with caution in patients with excessive bronchial secretions

Dose

Oral/intramuscular/intravenous

50–100 mg 4- to 6-hourly
To be given slowly when used IV
Maximum dose 400 mg/day and 600 mg/day in post-operative pain

Hepatic and renal impairment

↑ dose interval to 12 hours
Maximum dose 200 mg/day (not recommended in end-stage renal failure)

Equivalence and conversion

Morphine equivalence 1:5 (oral morphine 10 mg = oral tramadol 50 mg)

Mode of action

Non-selective MOP, KOP, and DOP receptor agonist
Inhibits neuronal noradrenaline reuptake and enhances serotonin (5-HT3) release (activation of descending serotonergic and noradrenergic pathways)

Tramadol-speci c side e ects

(For general opioid S/Es, see 7.1 Overview opioids, p. 119.)

Less respiratory depression, dependence, and constipation than other opioids
Rarely seizures, headaches
Associated with serotonin syndrome (rarely, may be precipitated if administered with SSRIs or SNRIs)
Anticholinergic S/Es (dry mouth, confusion, changes in BP), particularly in the elderly or patients on drugs acting on centrally acting NTs such as serotonin and noradrenaline

Pharmacodynamics

Cardiovascular: no signi cant e ects
Respiratory: RR, minute volume, partial pressure of carbon dioxide ($PaCO_2$) largely unchanged in therapeutic doses
GI: no e ect on bile duct contractility

Pharmacokinetics

Oral bioavailability: 68–100%
Vd: 2.9–4.37 L/kg; 20% protein-bound; 80% crosses the placenta
Metabolism: hepatic metabolism by cytochrome P450 isozymes CYP2B6, CYP2D6, CYP3A4 (85% is demethylated; O-desmethyltramadol is the only active metabolite)
Onset of action: 15 minutes. Peak plasma concentration 2 hours after PO; 12–15 hours with MR preparation

Duration of action: IR 6 hours, MR 12 hours
Clearance: 6.7–10.1 mL/kg/min
Elimination half-life: 4.5–7.5 hours
Excretion: 90% excreted in urine, 10% in faeces

Interactions

Precipitates when mixed with diazepam or midazolam

Co-administration with:

Quinidine: increases tramadol levels 50–60%
CYP3A4 inhibitors (ketoconazole, erythromycin) or inducers (St John's wort) alter tramadol levels
Digoxin: digoxin toxicity (rare reports)
SSRIs/SNRIs: serotonin syndrome
MAOIs and -2 adrenergic blockers increase seizure risk in animal studies
Triptans: potential for serotonin syndrome

Special circumstances

Pregnancy: avoid (embryotoxic in animals)
Breastfeeding: avoid (although amount likely too small to harm)

Additional information

Slowly removed by haemodialysis/haemo ltration
30% reversed by naloxone
Available with paracetamol: Tramacet®
Available with dexketoprofen: Skudexa®

Cost

Soluble/orodispersible tablets

Zydol®, Zamadol® 50 mg: £0.12–0.13/tablet (£3.60–31.00 per month, depending on dose)

Capsule (immediate-release)

Zamadol®, Zydol® 50 mg: £0.08/tablet (£2.50–19.00 per month, depending on dose)

Modi ed-release tablets/capsules

Tramadol hydrochloride MR non-proprietary, Invodol® SR, Mabron®, Maneo® 100 mg: £0.12–0.75/tablet (£7–90 per month)
Zamadol® 24-hour 150 mg: £0.38/tablet (£11 per month)
Maxitram®, Tramquel®, Zamadol® SR 100 mg: £0.20–0.24/tablet (£12–29 per month, depending on dose)

Oral drops

Tramadol hydrochloride non-proprietary 100 mg/mL: £0.35/mL (£35 per bottle)

Solution for injection

Tramadol hydrochloride non-proprietary, Zamadol®, Zydol® (100 mg/2 mL): £0.80–1.10 per ampoule

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7.13 Opioid rotation and conversion

Introduction

Opioid rotation is a technique where the type of an opioid is changed, in an attempt to reduce side e ects and maintain or enhance analgesia

Diminished analgesia can appear when an opioid is being used for longer due to tolerance

High doses of opioids can also contribute to OIH (increased sensitivity to painful stimuli)

Instead of increasing opioid doses, rotation to a di erent opioid can result in dose reduction, with improved analgesia and fewer S/Es

However, serious adverse events, including death, have been reported with opioid rotations

Most of the evidence on opioid rotations has been undertaken in cancer pain patients, although there is some evidence in CNCP. The heterogeneity of studies makes clinically useful comparison di cult

Physiological and pharmacological mechanisms

Individual variability to responses to opioids

Despite a clear understanding of the pharmacology of opioids, we have limited ability to predict an individual patient's response and S/Es

In cancer pain, 30% of patients fail to bene t from morphine, but many improve with other opioids

Many opioids (e.g. buprenorphine, fentanyl, oxycodone, codeine, tramadol) are metabolized via the CYP450 system (wide genetic variation, depending on liver function, other concomitant drugs a ecting the P450 pathway)

Mechanisms of incomplete cross-tolerance

Opioids have di erent levels of a nity and e cacy at MOP receptors, and high a nity of buprenorphine may displace the opioid it is replacing (initially increased risk of withdrawal when converting)

While most opioids act clinically as pure MOP receptor agonists, pethidine is also a DOP receptor agonist, while oxycodone, codeine, methadone, and pethidine are KOP receptor agonists. Tapentadol, tramadol, and methadone exert some of their actions via non-opioid receptors

Nearly 20 subtypes of the MOP receptor have been discovered, with di erent a nities to an opioid (the variability observed between opioids may be caused by MOP subtypes, at least partially)

Indications for an opioid rotation

Development of intolerable adverse e ects to an opioid (some evidence in cancer pain that an opioid rotation can reduce S/Es in up to 50% of patients)

Poorly controlled pain—some patients respond better to equipotent doses of di erent opioids

Patients with CNCP on high doses of opioids (normally oral morphine equivalent daily dose (oMEDD) >100 mg) who are not able to or who do not want to stop or reduce their doses of opioids, especially if the patient has risks of opioid-related adverse (particularly opioid-related respiratory impairment). These patients can be rotated to an opioid with a better safety pro le (e.g. from fentanyl patches to buprenorphine)

Development of renal or hepatic failure (some opioids have a better safety pro le, as outlined in 7.1 Overview of opioids, p. 119)

Opioid misuse and/or dependency—opioid replacement programmes (usually with methadone or buprenorphine) where opioids are provided in a controlled, safe, and monitored way under an addiction medicine service (in addiction medicine, opioid rotations are often not done with equipotent doses)

The need to change the route of delivery (e.g. cancer patients with dysphagia)

General principles of opioid conversion

Di erent onset times, especially between oral and transdermal opioids, as well as short- and long-acting formulations, need to be considered at initiation

Biopsychosocial factors, current medications, age, BMI, comorbidities, pain aetiology, chronicity, and renal and liver function in uence the method used during an opioid rotation and the patient response

The wide range of 'opioid equivalence' has led to the recommendation that a new opioid is started at 70% of the equipotent opioid dose to minimize the risk of inadvertent overdose (some studies quote a 50% dose equivalent reduction, particularly at high doses, in elderly/frail patients), due to incomplete cross-tolerance

Patients can access 1/6 to 1/12 of the background dose as breakthrough analgesia (the dose of breakthrough analgesia is normally a lower proportion of the background dose in patients on high doses of background opioids)

There is a risk that pain may are up or symptoms of opioid withdrawal may occur during an opioid rotation

There may be variability of the regimes or doses of opioids used during opioid rotations by clinicians in di erent settings. The opioid doses used are important, but even more important are a comprehensive patient assessment, individualized titrations according to response, and cautious monitoring of S/Es and e cacy

An individualized patient approach is needed

Opioid rotation should be recommended or supervised by an adequately trained and experienced health care practitioner

Withdrawal symptoms (e.g. sweating, yawning, abdominal cramps, restlessness, anxiety) occur if an opioid is stopped or the dose reduced abruptly

Patients need to be reviewed after an opioid rotation to assess the e cacy of the rotation, for titration of doses, and to ensure there are no opioid-related adverse e ects or S/Es. The timing of the review after an opioid rotation will depend on the clinical situation—some patients may require a review within 24 hours.

Opioid conversion

(See Tables 7.13.1, 7.13.2 and 7.13.3.)

A large number of opioid conversion charts exist in cancer and non-cancer pain, as well as several guidelines (e.g. in the BNF of the UK)

Signi cant variability between charts and often a signi cant range quoted for an equipotent dose on a number of these charts

Practical points for opioid conversion

1. Assess the patient thoroughly (uncontrolled pain secondary to worsening of an existing condition or due to a new cause)
2. Select the opioid that you want to convert to, and know the limitations of data available (1 + 1 does not always equal to 2 in opioid conversion)
3. Calculate the total dose of opioid that the patient takes (oral/parenteral/transdermal)
4. Calculate the OMEDD using the conversion factors shown in Tables 7.13.1, 7.13.2 and 7.13.3, and reduce the new dose by 20–30% to account for cross-tolerance

Example of rotating from oxycodone 20 mg orally to subcutaneous hydromorphone

1. Oral oxycodone 20 mg × 1.5 = oral morphine 30 mg
2. Oral morphine 30 mg / 5 = oral hydromorphone 6 mg
3. Oral hydromorphone 6 mg / 3 = SC hydromorphone 2 mg
4. Reduce by 20–30% to SC hydromorphone 1.5 mg:

i. Review the patient and plan regular follow-ups with careful monitoring (daily–weekly–monthly, more frequently for cancer patients; psychological support may be needed)
ii. In opioid rotation, consider the half-life of the current opioid and the time of onset of action of the new opioid, to avoid breakthrough pain and opioid toxicity (e.g. fentanyl patch to tapentadol: do not use tapentadol until 24 hours after removal of the fentanyl patch)

Table 7.13.1 Equipotent oral opioid doses

Opioid	Equivalent oral doses	Potency in comparison to oral morphine (conversion factor)	Oral:parenteral ratio
Hydromorphone	2 mg	5	3:1
Oxycodone	6.6 mg	1.5	2:1
Morphine	10 mg	1	3:1
Tapentadol	25 mg	0.4	N/A
Tramadol	100 mg	0.1	1.2:1
Dihydrocodeine	100 mg	0.1	N/A
Codeine	100 mg	0.1	2:1

Table 7.13.2 Transdermal opioid patches (conversion from oral morphine)

Oral morphine (mg/day)	12	48	84	Side e ects
Buprenorphine patch (mcg/hour)	5	20	35	In 17% (nausea and vomiting in 6.7%)
Oral morphine (mg/day)	30	60	120	Side e ects
Fentanyl patch (mcg/hour)	12	25	50	In 20% (nausea and vomiting in 10%)

Avoid direct conversion of oral morphine >80 mg to buprenorphine—risk of opioid withdrawal.

Table 7.13.3 Equipotent intravenous opioid doses (e.g. perioperative use)

Opioid	Equivalent IV doses	Potency
Sufentanil	10–20 mcg (0.01–0.02 mg)	500–1000
Remifentanil	50 mcg (0.05 mg)	100–200
Fentanyl	100 mcg (0.1 mg)	100
Alfentanil	1 mg	10
Hydromorphone	2 mg	5
Oxycodone	7 mg	1.5
Morphine	10 mg	1
Pethidine	75 mg	0.15
Tramadol	100 mg	0.1
Codeine	100 mg	0.1

Opioid rotation to methadone (see also 7.6 Methadone, p. 136)

Methadone = second-line opioid for pain management (NMDA receptor activity is thought to be responsible for lower tolerance)

Conversion to methadone is not linear due to its pharmacokinetic pro le

There is no consensus on the best regime for an opioid rotation to methadone

Opioid rotations to methadone are not routinely done for pain management due to its complexities, risks, and pharmacological properties. Depending on the conversion ratio and dosing regimen used, there is a broad range in the doses of methadone

Methadone is mostly used by pain specialists as an adjuvant

Input from a specialist in palliative care or addiction medicine or an experienced practitioner is recommended

Steps to do an opioid rotation to methadone

1. Consider factors described above in an opioid rotation and speci c factors for methadone (e.g. risks of QTc prolongation/cardiac arrhythmias, drug interactions, ability to monitor patient closely, respiratory disease, and other factors discussed in 7.6 Methadone p. 136))
2. Calculate the current OMEDD and the equivalent dose of methadone. This can be done using the Ayonrinde or Mercadante or Ripamonti conversion ratios (see Table 7.6.1 in 7.6 Methadone, p. 137)
3. Determine the dosing regimen using one of the following protocols:

Morley–Mankin regime (better for inpatients)

Day 1: stop previous opioid. Commence methadone dose equivalent to 10% of the OMEDD (highest amount 30 mg) PRN 3-hourly

Day 6: provide average methadone dose used on days 4 and 5 in two divided doses (12-hourly) and methadone PRN at 10–15% of the new methadone background dose

Friedman regime

Takes into account the patient's age, more conservative at lower doses

Stop previous opioid and then:

Patients <65 years on OMEDD <1000 mg: use **10%** of the OMEDD

Patients >65 years on OMEDD <1000 mg or any patient of any age on OMEDD 1000–2000 mg: use **5%** of the OMEDD

Patients on OMEDD >2000 mg: use **3%** of the OMEDD

Methadone product information

Daily dose of oral methadone is determined as a percentage of the OMEDD:

OMEDD of <100 mg: methadone dose of 20–30% of the OMEDD

OMEDD of 100–300 mg: methadone dose of 10–20% of the OMEDD

OMEDD of 300–600 mg: methadone dose of 8–12% of the OMEDD

OMEDD of 600–1000 mg: methadone dose of 5–10% of the OMEDD

OMEDD of >1000 mg: methadone dose of <5% of the OMEDD

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CHAPTER 8

Non-steroidal Anti-in ammatory Drugs and Paracetamol

Peter Keogh

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8.1 Overview of non-steroidal anti-in ammatory drugs

Introduction

NSAIDs refer to both non-selective NSAIDs (nsNSAIDs) and COX-2 inhibitors

Widely used to treat mild pain as a monotherapy or as a co-analgesic to treat moderate to severe pain

Indications

Acute pain, subacute pain, chronic pain, cancer-related pain

Perioperatively, burns, trauma, MSK pain, or conditions with an in ammatory component (e.g. in ammatory phase of CRPS, rheumatoid arthritis (RA), scleroderma, ankylosing spondylitis)

Co-analgesic as part of a multimodal regimen for moderate to severe pain

Adjunct for opioid-sparing e ects and potential reduction of opioid-related adverse e ects

Some headache disorders

Antipyretic

Classi cation

Salicylic acids: aspirin

Acetic acid derivatives: indometacin, diclofenac, ketorolac

Fenamates: mefenamic acid

Pyrazolones: phenylbutazone

Propionic acids: ibuprofen, naproxen

Oxicams: piroxicam, meloxicam

Physiology of cyclo-oxygenase enzymes

Within the phospholipid bilayer of cell membranes, phospholipase A2 stimulates the production of arachidonic acid precursor. Prostaglandin precursor formation from arachidonic acid is catalysed by COX enzymes which, in turn, produces TXA2, PGI2, and in ammatory

PGs (PGE2, PGF2 , PGD2). Pro-in ammatory leukotrienes are also produced via an alternate lipoxygenase pathway catalysed by 5-lipoxygenase enzyme. There are three COX isoenzymes:

COX-1 (the constitutive form) is blocked by nsNSAIDs and aspirin. COX-1 is largely responsible for the production of:

- Cytoprotective PGs—gastric mucosal protection
- TXA2—promotes platelet aggregation, vasoconstriction

COX-2 (the inducible form) is blocked by nsNSAIDs, aspirin, and COX-2 inhibitors. COX-2 is largely responsible for the production of:

- In ammatory PGs—stimulate production of in ammatory mediators which sensitize peripheral and/or central nociceptors
- Prostacyclin—Prevents platelet aggregation, vasodilatation, and regulation of renal blood ow

COX-3—its existence is controversial. May be involved in the mechanism of action of paracetamol

Mechanism of action

NSAIDs inhibit the COX pathway, reducing the production of PG precursors. The di erential between COX-1 and COX-2 inhibition determines the e ect and is measured by the drug's selectivity ratio

Inhibition of the COX-2 pathway results in the following:

- Anti-in ammatory e ect: decreased PG and prostacyclin causes vasodilatation, resulting in decreased tissue oedema
- Analgesia: decreased sensitization of nociceptive nerve endings by decreased production of PGs and in ammatory mediators such as bradykinins. NSAIDs are e ective in headaches by decreasing PG-induced vasodilatation
- Antipyretic e ect: decreased secretion of in ammatory mediators, such as IL1, which elevate body temperature by acting on the hypothalamus

Routes of administration

Topical, rectal, PO, IM, and IV routes

Topical NSAIDs may be associated with fewer S/Es

Pharmacokinetics

Absorption: NSAIDs are weak acids (pKa = 3–5) and rapidly absorbed from the stomach. Slow-release preparations are available

Distribution: highly protein-bound (>90%), with potential to displace other protein-bound drugs

Metabolism: hepatic. Oxidation and conjugation to inactive metabolites

Excretion: mainly in the urine, variable amount in bile

Adverse e ects

More predominant in the elderly, those with comorbidities, and those on NSAIDs which are less COX-2-selective

All NSAIDs share to di erent degrees similar mechanistic-based adverse e ects

Nervous system: increased risk of ischaemic stroke—higher risk with COX-2-selective NSAIDs. Rarely headaches, dizziness, drowsiness, insomnia, vertigo, and tinnitus

CVS: increased risk of MI, independent of baseline cardiovascular risk factors. Higher risk with COX-2-selective NSAIDs. Risks negated with naproxen (up to 1 g daily) and ibuprofen (up to 1.2 g daily). Can also contribute to development of hypertension and pulmonary oedema

Respiratory system: bronchospasm (increased activity in the lipoxygenase pathway)

GI system: peptic ulceration, diarrhoea, bleeding—consider enteric-coated formulations, administration with food, and antacid prophylaxis. Slight elevation in hepatic transaminases is common

Renal system: dysfunction and failure from decreased renal blood ow, decreased GFR, salt and water retention, acute papillary necrosis, and chronic interstitial nephritis

Coagulation: prolongation of bleeding via inhibition of platelet function (COX-1-mediated)

Skin hypersensitivity, rash, angio-oedema, urticaria, photosensitivity

Soft tissue healing: animal studies have shown impaired wound healing by blocking the release of PGs which promote angiogenesis and mediators involved in wound healing. Clinical studies have not identi ed strong evidence indicating poorer wound healing or anastomotic breakdown

Bone healing: PGs stimulate osteoblastic and osteoclastic activity. Animal models have shown decreased bone healing with inhibition of PG production. Clinical use of NSAIDs in bone fractures remains controversial

Contraindications

NSAID-induced hypersensitivity (history of precipitation of asthma, angio-oedema, urticaria, or rhinitis), GI ulceration/bleeding, renal impairment (moderate/severe), major vascular/cardiac surgery, major surgery with a previous history of a thrombotic event (stroke and MI), hypovolaemia, moderate/severe heart failure

Pregnancy, especially in the third trimester, is associated with an increased risk of closure of the fetal ductus arteriosus *in utero*. Regular use of NSAIDs in early pregnancy is associated with an increased risk of miscarriage

NSAIDs are not readily excreted in breast milk. Most manufacturers advise caution during breastfeeding and to avoid aspirin use altogether (risk of neonatal Reyes syndrome)

Analgesic e cacy

A single dose of an NSAID has similar analgesic activity to paracetamol

NSAIDs have to be used in combination with other agents for moderate to severe pain

Full analgesic e ect should be obtained within a week of initiation of regular NSAID use, but full anti-in ammatory e ects may take up to 3 weeks to take e ect

The di erences in anti-in ammatory properties between NSAIDs are small, but there is considerable variation in individual response to these drugs

Sixty per cent of patients respond to any NSAID, and non-responders may respond to another NSAID

Ibuprofen has fewer adverse e ects than other nsNSAIDs, but its anti-in ammatory properties are weaker

Naproxen combines good analgesic and anti-in ammatory e cacy, with a low (but higher than ibuprofen) incidence of adverse e ects

Diclofenac has similar e cacy to naproxen, but a higher incidence of adverse e ects

Acute pain

NSAIDs form an integral part of multimodal analgesic regimes

Combined use of NSAIDs and paracetamol is more e ective than using NSAIDs or paracetamol alone

Normally, opioid use is reduced by 30–50% when NSAIDs are also used

NSAID use reduces the incidence of pneumonia, admission to critical care, and ventilation support in patients with rib fractures

Chronic non-cancer pain

Limited evidence supports NSAIDs in chronic back pain and osteoarthritis (OA)

NSAIDs have a role in in ammatory joint conditions such as RA

NSAIDs probably have no role in neuropathic pain

Cancer-related pain

Use may be associated with a survival advantage in a range of solid cancers through an as yet unknown mechanism

Additional information

When prescribing NSAIDs, take into account the patient's individual risk factors and potential bene ts

Prescribe the lowest e ective dose for the shortest possible time

Patients should be counselled on the risk of NSAID use, and reviewed regularly

Exercise caution in patients who are elderly and have cardiovascular risk factors, diabetes, uncontrolled hypertension, renal dysfunction, major surgery, advanced hepatic impairment, prior history or risk of GI ulceration, and coagulation defects (COX-2 inhibitors may be an acceptable alternative)

NSAIDs are highly protein-bound and can displace other drugs from plasma proteins. Of note:

- Increased risk of bleeding when given with SSRIs, selective SNRI, aspirin, warfarin, and other anticoagulants
- Enhanced risk of lithium toxicity
- Interactions also with corticosteroids, ACEIs, potassium-sparing diuretics, aminoglycosides, and methotrexate

Ibuprofen is the most appropriate nsNSAID for use in children

Naproxen (up to 1 g/day) or ibuprofen (up to 1.2 g/day) are recommended as rst-line drugs for adults, based on cardiovascular risk

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8.2 Cyclo-oxygenase 2 inhibitors

Introduction

Selective COX-2 inhibitors were developed to decrease the risk of GI adverse e ects mediated via COX-1 enzyme inhibition by nsNSAIDs

The analgesic e cacy of COX-2 inhibitors is similar to that of nsNSAIDs

Classi cation

Pyrazole: parecoxib, celecoxib, rofecoxib

Methylsulphone: etoricoxib

Phenylacetic acid derivative: lumaricoxib

Mechanism of action

COX-2 inhibitors reduce the production of PGs which facilitate the in ammatory response to tissue injury

Less COX-1 inhibition than nsNSAIDs. This has theoretical advantages by maintaining production of protective PGs responsible for positive e ects in relation to gastric mucosal protection, platelet function, and renal blood ow

The interdependence between COX-1 and COX-2 inhibition in uences the risks and bene ts of di erent NSAIDs. This is measured by the drug selectivity ratio (e.g. the selectivity ratio for celecoxib is 1:30, etoricoxib 1:344, and parecoxib 1:61)

Characteristics of COX-2 inhibitors versus non-selective NSAIDs

Modest reduction in serious GI adverse events

Decreased bleeding (do not signi cantly impair platelet function)

Probably less bronchospasm in asthmatics

Similar analgesic e cacy

Similar risk of renal impairment

Similar rates of cardiovascular adverse e ects (stroke and MI). Celecoxib and naproxen are associated with the lowest risk

More expensive

Routes of administration and dosing

Celecoxib: 200–400 mg PO daily in 2 divided doses 12 hourly (not recommended in children)

Etoricoxib: 30–90 mg PO once daily

Parecoxib: IM or IV injection up to 40 mg daily (some sources do not recommend in children)

Pharmacokinetics

Celecoxib:

- Absorption: good oral bioavailability
- Distribution: 97% protein-bound, Vd 5.7 L/kg
- Metabolism: hepatic by CYP2C9 to inactive metabolites
- Excretion: renal. Elimination t1/2: 8–12 hours

Etoricoxib:

- Absorption: oral bioavailability 95%
- Distribution: 90% protein-bound, Vd 1.5 L/kg

Metabolism: hepatic by CYP3A4 and other cytochrome P450 enzymes to inactive metabolites

Excretion: renal. Elimination t1/2: 22 hours

Parecoxib:

Absorption: poor oral bioavailability. Given IM or IV

Distribution: 99% protein-bound

Metabolism: hepatic conversion of prodrug to valdecoxib, and then by CYP2C9 and CYP3A4 to inactive metabolites

Excretion: renal. Elimination t1/2: 8 hours

Additional information

Rofecoxib was withdrawn from the UK in 2004 over cardiovascular safety concerns. The APPROVe study (2005) showed an increased cardiovascular risk when it was used in patients with a history of colorectal adenomas

Valdecoxib was withdrawn in the UK in 2005 because of serious skin reactions

Lumiracoxib was withdrawn in the UK in 2007 because of hepatotoxicity

VIGOR study (2000): patients with RA treated with rofecoxib had fewer upper GI events than those treated with naproxen

PRECISION study (2016): celecoxib was non-inferior to ibuprofen or naproxen with regard to cardiovascular adverse e ects

Further reading

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2. Husband M, Mehta V. Cyclo-oxygenase-2 inhibitors. Contin Educ Anaesth Crit Care Pain 2013;13(4):131–5
3. Moore RA, Derry S, Aldington D, Wi en PJ. Single dose oral analgesics for acute postoperative pain in adults—an overview of Cochrane reviews. Cochrane Database Syst Rev 2015;9:CD008659

8.3 Diclofenac

Chemical

A phenylacetic acid derivative

Presentation

Tablets: immediate-release, 25 mg and 50 mg; modi ed-release, 75 mg and 100 mg

Suppositories: 12.5 mg, 25 mg, 50 mg, and 100 mg

IV or IM injection: 25 mg/mL and 37.5 mg/mL

Topical gel: diclofenac sodium 1%

Others: dermal patch, eye drops, preparations combined with misoprostol

Mechanism of action and important features

Non-selective COX inhibitor

Number needed to treat (NNT) (50%) 50 mg = 2.7

Routes of administration and dosing

Pain in adults:

PO: 25–50 mg every 6–8 hours (maximum 150 mg daily)

IV or IM injection: 50–75 mg every 4–6 hours (maximum 150 mg daily)

Rectally: 75–150 mg daily in divided doses

Pain in children:

PO: >1 year old, 1.5–2.5 mg/kg (maximum 50 mg) three times daily

IV or IM injection: >2 years old, 0.3–1 mg/kg 1–3 times daily (maximum 150 mg daily)

Rectally: not licensed for <6-year olds, except if >1 year old with juvenile idiopathic arthritis; 8–12 kg, 12.5 mg twice daily, and >12 kg, 1 mg/kg (maximum 50 mg) three times daily

Pharmacokinetics

Absorption: oral bioavailability 60%

Distribution: protein-bound 99%, Vd 0.12–0.17 L/kg

Metabolism: hepatic, predominantly by hydroxylation and methylation, resulting in several phenolic metabolites which are converted to glucuronide conjugates. Two of these metabolites are biologically active, but to a much smaller extent than diclofenac. A small proportion of the metabolism is by glucuronidation of the intact molecule

Excretion: 60% as metabolites in the urine, 1% unchanged in the urine, and 40% as metabolites in bile. Elimination t1/2: 1.1–1.8 hours

Cost

50 mg (28 tablets): £1.63

50 mg (ten suppositories): £2.04

Gel 1.16% (100 g): £4.63

75 mg for IV injection (ten ampoules): £9.91–24.00

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Electronic Medicines Compendium. Diclofenac potassium 50 mg tablets. https://www.medicines.org.uk/emc/medicine/24377
3. Peck T, Hill S, Williams M. Pharmacology for Anaesthesia and Intensive Care. 3rd edition, 2008. Cambridge: Cambridge University Press

8.4 Ibuprofen

Chemical

Phenylpropionic acid derivative

Presentation

Tablets, capsules, and caplets (immediate-release) 200 mg and 400 mg

Tablets (modi ed-release) 800 mg

Oral suspension 100 mg/5 mL
Topical gel 5% and 10%
IV preparation 800 mg/8 mL
Aqueous cream 10 mg/mL with isopropyl myristate
Combined with codeine, paracetamol, phenylephrine, and pseudoephedrine

Mechanism of action and important features

Non-selective COX inhibitor
Acute pain NNT (50%) 400 mg = 2.5
Anti-in ammatory properties are weaker than those of other nsNSAIDs
Increased risk of myocardial thrombotic events minimized up to 1.2 g daily

Routes of administration and dosing

Adults: 400–800 mg 3–4 times daily (maximum 2.4 g daily or <3.2 g for 2 days)
Children: maximum 30 mg/kg in 3–4 divided doses. In the UK, not licensed in children aged under 3 months or if body weight below 5 kg

Pharmacokinetics

Absorption: oral bioavailability 87–100%
Distribution: 99% protein-bound. Vd 0.14 L/kg
Metabolism: hepatic. Predominantly by hydroxylation and conjugation to inactive metabolites (metabolites A and B)
Excretion: renal; 10% unchanged in the urine. Elimination t1/2: 1.3–3 hours

Additional information

Ibuprofen is the most appropriate nsNSAID for use in children
Dexibuprofen is the active enantiomer of ibuprofen. It has similar properties to ibuprofen and is licensed for the relief of mild to moderate pain and in ammation

Cost

48 tablets of 400 mg for as little as £1.20
Ibuprofen suspension 100 mg/5 mL: £1.59

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Electronic Medicines Compendium. Ibuprofen. https://www.medicines.org.uk/emc/search?q=%22Ibuprofen%22

8.5 Naproxen

Chemical

Phenylacetic acid derivative

Presentation

Tablets (immediate-release) 250 mg and 500 mg
Oral suspension 25 mg/mL
Preparations combined with esomeprazole and misoprostol

Mechanism of action and important features

Non-selective COX inhibitor
NNT (50%) 500 mg = 2.7
Increased risk of myocardial thrombotic events minimized up to 1 g daily

Routes of administration and dosing

Pain in adults:

PO: 500 mg initially, then 250 mg every 6–8 hours as required (maximum dose after first day 1.25 g daily)

Pain in children:

PO: 5 mg/kg twice daily (maximum 1 g daily)

UK—not licensed in children aged under 5 years for juvenile idiopathic arthritis or those under 16 years for musculoskeletal pain or dysmenorrhoea

Pharmacokinetics

Absorption: oral bioavailability 95%
Distribution: 99% protein-bound. Vd 0.16 L/kg
Metabolism: hepatic to 6-0-desmethyl naproxen and other conjugated metabolites
Excretion: in the urine (97%) and faeces (3%). Elimination t1/2: 12–17 hours

Cost

56 tablets of 250 mg: £2.20 (gastroresistant)
28 tablets of 250 mg: £2.91 (monthly approximately £6)
28 tablets of 500 mg: £2.47 (monthly approximately £5)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Electronic Medicines Compendium. Boots period pain relief 250 mg gastro-resistant tablets. https://www.medicines.org.uk/emc/medicine/26017

8.6 Paracetamol

Indications

Analgesia for mild to moderate pain
Antipyretic

Chemical

Acetanilide derivative

Presentation

Tablets, capsules, and caplets (immediate-release) 500 mg

Oral suspension 120 mg, 250 mg, and 500 mg/5 mL

Suppositories 60 mg, 120 mg, 125 mg, 200 mg, 250 mg, 500 mg, and 1 g

IV infusion 10 mg/mL

Also available in modi ed-release preparations

Combined with codeine, tramadol, isometheptene mucate, buclizine, ca eine, and metoclopramide

Mechanism of action

Poorly understood. Several proposed mechanisms:

PG inhibition: inhibition of PG synthesis by weak inhibition of peripheral COX activity, with apparent selectivity for COX-2. It is also believed to work by COX-1 variant inhibition

Serotonergic pathway activation: enhanced descending inhibition pathways via 5-HT3 receptor agonism

Endocannabinoid enhancement: reuptake inhibition of endocannabinoids via N-arachidonoyl phenol amine, a conjugated metabolite of paracetamol, which is implicated in the activation of TRPV1 receptors, inhibition of nitric oxide

Routes of administration and dosing

Pain in adults:

PO: 0.5–1 g every 4–6 hours (maximum 4 g daily)

IV infusion:

Adults over 50 kg: 1 g every 4–6 hours (maximum 4 g daily)

Adults up to 50 kg: 15 mg/kg every 4–6 hours (maximum 60 mg/kg daily)

Rectally: 0.5–1 g every 4–6 hours (maximum 4 g daily)

Pain in children:

PO: 1 month to 18 years 15–20 mg/kg (maximum 1 g) every 4–6 hours, maximum 75 mg/kg daily (maximum 4 g) in divided doses

Dose should be based on lean body weight, and not on total body weight, in obese children

Pharmacokinetics

Absorption: oral bioavailability 70–90%. Rectal bioavailability 68–88%

Distribution: 0–5% protein-bound. Vd 1 L/kg. Non-ionized at physiological pH, with good lipid solubility and CNS penetration

Metabolism: hepatic. Predominantly by glucuronidation and sulphation to non-toxic conjugates. Small amount oxidized via cytochrome P450 enzyme system to highly toxic N-acetyl-p-benzo-quinone imine (NAPQI). NAPQI is rapidly conjugated with hepatic glutathione to render it harmless

Excretion: 2–5% unchanged in the urine. Elimination t1/2: 1.9–2.2 hours

Pharmacodynamics

CNS: analgesia, antipyretic through direct action on the hypothalamus

Hepatic: hepatotoxic in overdose

Adverse e ects and toxicity

CNS: possible sedation

CVS: hypotension and ushing with IV infusion

Respiratory system: bronchospasm

GI: non-speci c GI symptoms

Hepatic: hepatocellular necrosis in overdose. Following a toxic dose, normal hepatic conjugation pathways become saturated. When hepatic glutathione stores are depleted, NAPQI accumulates. NAPQI forms covalent bonds with sulfhydryl groups in hepatocytes, resulting in centrilobular hepatic necrosis. Treatment is with oral methionine or PO or IV acetylcysteine to provide a source of glutathione

Renal: acute tubular necrosis in overdose

Haematological: thrombocytopenia, leucopenia, neutropenia

Skin: rash

Contraindications

Hypersensitivity to the active substance or to any of the excipients

Caution in those allergic to aspirin—5% cross-sensitivity

Caution in renal ± hepatic impairment and malnourished

Interactions

Enzyme-inducing drugs may increase the risk of paracetamol toxicity

Co-administration of paracetamol (4 g/day for at least 4 days) with oral anticoagulants may lead to slight variations in international normalized ratio (INR) values

Probenecid causes an almost 2-fold reduction in clearance of paracetamol

Additional information

Pregnancy: not known to be harmful

Breastfeeding: clinically insigni cant amounts excreted in breast milk

Cost

500 mg (16 tablets): £0.77 (even as little as £0.13)

Ten suppositories of 500 mg: £36.50

Oral suspension 120 mg/5 mL for 100 mL bottle: £2.29

Further reading

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3. Sharma C, Mehta V. Paracetamol: mechanisms and updates. Contin Educ Anaesth Crit Care Pain 2014;14(4):153–8

CHAPTER 9

Anticonvulsants

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9.1 Overview of anticonvulsants

Introduction

Anticonvulsants reduce the excitability of neurons and hence are important components of multimodal management of neuropathic pain

Approximately 60% of prescriptions for this group of medications are for non-epilepsy reasons

They help in reduction of the intensity of pain, as well as improve sleep and decrease anxiety

Opioid-sparing e ect, hence a useful adjunct in perioperative and acute pain

Classi cation

(See Table 9.1.1.)

Table 9.1.1 First- and second-generation of anticonvulsants

First generation	Second generation
Older, more side e ects Examples: carbamazepine, phenytoin, sodium valproate, benzodiazepines	Newer, better side e ect pro le Examples: gabapentinoids, lamotrigine, topiramate, oxcarbazepine

Mode of action

Blockade of Na^+ channels, e.g. carbamazepine, oxcarbazepine (OXC), phenytoin, lamotrigine, topiramate

Blockade of Ca^{2+} channels, e.g. gabapentinoids, lamotrigine, topiramate

Decreased transmission of glutamate via AMPA receptors, e.g. topiramate

Modulation and potentiation of GABA via inhibitory GABA receptors, e.g. BZDs, topiramate

Indications

Treatment of epilepsy

Treatment of neuropathic pain (neuralgia, MS, post-sympathectomy pain, neuropathic cancer pain, post-traumatic neuralgia, PHN, post-stroke pain, painful diabetic neuropathy, HIV, chemotherapy-induced neuropathic pain)

Fibromyalgia, anxiety disorders

Migraine

Analgesic e cacy—pharmacotherapy for neuropathic pain

Gabapentinoids: high evidence, moderate e ect size on pain, as well as on QoL, tolerability/safety (high for gabapentin and moderate for pregabalin). First line for neuropathic pain—overall NNT: pregabalin 7.7 (6.5–9.4) and gabapentin 6.3 (5.0–8.3)

Carbamazepine—NNT: 1.7 (1.3–2.2) for trigeminal neuralgia (TN); 2.3 (1.6–3.9) for diabetic neuropathic pain; 3.4 (1.7–105) for post-stroke pain

Phenytoin—NNT: 2.1 (1.5–3.6) for diabetic neuropathic pain

Lamotrigine—NNT: 2.1 (1.3–6.1) for TN, 4.0 (2.1–42) for diabetic neuropathic pain

Topiramate—NNT: 7.4 (4.3–28.5) for diabetic neuropathic pain, with high withdrawal rate

Additional information

Should be considered in patients who have peripheral or central neuropathic pain and some chronic widespread pain syndromes

Lowest possible dose to be started and titrated up slowly to balance between e ect and S/Es

Should intolerable S/Es occur, titrate down to the least e ective dose which is tolerated by the patient

Lower doses in the elderly, and in renal and hepatic impairment due to decreased excretion

Avoid in pregnancy and breastfeeding if possible (for pain)

Further reading

1. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73
2. Tracey I. Pain 2012 Refresher Courses. 14th World Congress on Pain, 2012. Seattle, WA: IASP Press

9.2 Overview of benzodiazepines

Introduction

BZDs are a group of drugs used to treat anxiolysis, in turn helping with pain management

They are used in anaesthesia such as hypnotics and anxiolytics, and help as premedication

Used as anticonvulsants, especially for management of acute seizures

Classi cation of benzodiazepines

Short-acting (up to 6 hours): midazolam, oxazepam

Intermediate-acting (6–12 hours): lorazepam, temazepam, alprazolam, nitrazepam

Long-acting (12 hours to 3 days): diazepam, clonazepam (see 13.7 Clonazepam, p. 242)

Mechanism of action

$GABA_A$ receptor agonist (by allosteric modulation) at speci c BZD binding site (subunit)
Increase in ux and conductance of chloride ion, causing hyperpolarization of the neuronal cell membrane (in the presence of GABA NT)
E ective CNS depression and muscle relaxation, anxiolytic e ects

Indications

Muscle spasm
Pain-associated anxiety
Acute back pain
Lancinating neuropathic pain
Case studies showing promise in phantom limb pain (clonazepam)
Some evidence of BZDs being helpful in tic douloureux, tension headache, and temporomandibular joint disorder
Insomnia

Contraindications/caution

Alcohol excess
Severe depression
High falls risk
Concurrent sedative drug use (e.g. opioids)
Acute angle closure glaucoma
Obstructive sleep apnoea

Dose

Minimal e ective dose titrated to e ect. Avoid sudden increases in dose to prevent oversedation; exact dose varies with agent
Diazepam: initially PO 2–10 mg daily in divided doses
Clonazepam: 1–2 mg daily in 3–4 divided doses
Aim for gradual weaning in long-term users

Side e ects

Excessive sedation, confusion, paradoxical aggression/stimulant e ect
Allergic reaction
Tolerance, dependence, and withdrawal
Amongst chronic pain users, BZD use is associated with:
- Greater pain severity
- Higher risk of strong opioid use
- Substance abuse
- Greater mental health comorbidity
- Increased emergency health care consultation

Interactions

Aim to avoid any concurrent CNS depressant
Barbiturates, alcohol, opioids, baclofen
Antipsychotic agents

Special circumstances

Pregnancy: weak evidence to suggest association between BZDs and cleft lip and palate, hence best to avoid in pregnancy. Risk of neonatal withdrawal symptoms

Breastfeeding: considered safe in breastfeeding if <20 mg per 24 hours

Warn patients about the potential risks when driving and operating machinery

Will need to contact the Driver and Vehicle Licensing Agency (DVLA) regarding driving

Can precipitate hepatic encephalopathy in hepatic failure

Increased cerebral sensitivity in renal patients

Additional information

Generally well tolerated if used cautiously

No routine blood concentration monitoring in practice

Used mainly for non-pain-related reasons (anxiolytics, insomnia, sedation)

Occasionally, paradoxical disinhibition is experienced

Based on current evidence, BZDs cannot be recommended for neuropathic pain

Published case reports of clonazepam successfully used in phantom limb pain

Flumazenil—reverses BZD e ect when given IV in 100 mcg increments. It has a short t1/2 of 1 hour, can precipitate seizures

Diazepam—long-acting benzodiazepine

Used as muscle relaxant in chronic pain

Pharmacokinetics (diazepam)

Absorption: rapid gut absorption e ective within 15 minutes, 85–100% bioavailability

Distribution: highly protein-bound (98%), peak plasma concentration in 30–90 minutes

Metabolism: main active metabolite is desmethyldiazepam; other active metabolites are temazepam and oxazepam. Metabolites undergo glucuronidation and are then excreted in the urine

Excretion: t1/2 30–60 hours

Cost

2 mg (28 tablets): £0.57

5 mg (28 tablets): £0.69

10 mg (28 tablets): £0.75

Further reading

1. Masada M, Smith S. Drugs in Anaesthesia and Intensive Care. 1st edition, 2003. Oxford: Oxford University Press
2. Jacob S, Nair A. An updated overview on therapeutic drug monitoring of recent antiepileptic drugs. Drugs R D 2016;16(4):303–16
3. Nielsen S, Lintzeris N, Bruno R, et al. Benzodiazepine use among chronic pain patients prescribed opioids: associations with pain, physical and mental health, and health service utilization. Pain Med 2005;16:356–66

9.3 Gabapentin

Class of drugs

Gabapentin gel 6% (2–10%)

Acetic acid derivative

Indications

First-line treatment for painful diabetic neuropathy and PHN

Fibromyalgia, anxiety, restless legs syndrome, hot ushes, insomnia

Facial pain, episodic migraine

Epilepsy (partial seizures)

Perioperative pain due to its opioid-sparing e ects

Gel for focal neuropathic pain and localized itch

Contraindications/caution

Diabetes mellitus—worsening glycaemic control

Manufacturers advise caution in adolescents and patients with low body weight

Dose

Doses start at 100 mg three times daily up to a maximum of 1200 mg three times daily (3600 mg/day)

Avoid sudden withdrawal. Aim for dose reduction to stop over 14 days or more

NNT previously was 4.3–4.7 across all neuropathic conditions, but updated to 9.6

Mode of action

Although structurally similar to GABA, the mode of action is predominantly by binding to voltage-sensitive Ca^{2+} channels in the CNS and peripheral nervous system, with a 3-fold response:

- Antagonism of NMDA on glutamate receptors
- Enhanced action of glutamate decarboxylase, thereby increasing GABA production
- Enhances release of GABA at synapses

All responses lead to hyperpolarization of the neuron and inhibit AP propagation

Monitoring

Monitoring is possible with gabapentin assays. Most patients respond at a therapeutic level of 2–20 mcg/mL

Monitor for weight gain

Side e ects

Neurological: ataxia, dizziness, drowsiness, fatigue, diplopia, nystagmus, and tremor

GI: abdominal pain, constipation, dyspepsia, and nausea and vomiting

Weight gain and peripheral oedema

Pharmacokinetics

Absorption: slowly from the gut with unpredictable pharmacokinetics, with peak plasma concentration occurring within 3–4 hours; duodenal absorption limited by transporter saturation (LAT1 transporter).

Bioavailability not linear (note: di erent characteristic to pregabalin which shows rst-order absorption—concentration is linearly dose-dependent)

900 mg/day = 60%
1200 mg/day = 47%
2400 mg/day = 34%
3600 mg/day = 33%
4800 mg/day = 27%

Distribution: minimal plasma protein binding (<3%)
Metabolism: negligible
Excretion: renally as unchanged drug
Elimination t1/2: 5–7 hours
Gabapentin is excreted mainly unchanged by renal mechanism; important to reduce doses in renal impairment:

Maximum 1.8 g/day if estimated GFR (eGFR) 50–80 mL/min
Maximum 900 mg/day if eGFR 30–50 mL/min
Maximum 600 mg/day if eGFR 15–30 mL/min
Maximum 300 mg/day if eGFR <15 mL/min

Interactions

Use cautiously with opioids—can potentiate sedation
Known interactions alter seizure threshold but do not a ect pain management
Bioavailability is reduced with simple antacids

Special circumstances

Pregnancy: use with caution if bene t outweighs risk
Breastfeeding: use with caution if bene t outweighs risk
Children: unlicensed use in those aged <6 years. Dose: 10 mg/kg, maximum 70 mg/kg. If used with opioids, rare risk of severe respiratory depression, as well as increased emotional and behavioural S/Es
Elderly: increased cognitive S/Es, hence lower doses to be used. Care in renal impairment

Additional information

Not e ective in HIV-induced neuropathy or CRPS

Cost

100 mg capsules (100 pack): £2
300 mg capsules (100 pack): £3.20
600 mg tablets (100 pack): £8.72
Monthly supply of 100–1200 mg three times daily: £2–17.50
50 mg/mL in 150 mL bottle (= 250 mg three times daily for 1 month): £57–67
Gabapentin gel (prepared by pharmacy): £0.50–2.41 per gram

Further reading

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2. Moore RA, Wi en PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and bromyalgia in adults. Cochrane Database Syst Rev 2014;4:CD007938
3. Bockbrader H, Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet 2010;49(10):661–9

9.4 Pregabalin

Class of drug

3-isobutyl derivative of gamma-amino butyric acid (GABA)

Indications

Chronic and acute neuropathic pain

PHN

Generalized anxiety disorder—licensed use

Contraindications/caution

Pregnancy—folic acid inhibition and neural tube defects

Dose

Dose started at 150 mg/day in divided doses, increasing slowly to a maximum of 600 mg/day over a few weeks

Lowest NNT for 50% reduction in pain with 600 mg of pregabalin daily: PHN, 3.9; diabetic neuropathy, 5.6; central neuropathic pain, 5.6; and bromyalgia, 11

Mode of action

Mechanism similar to that of gabapentin, with binding of voltage-gated Ca^{2+} channels and release inhibition of excitatory NTs in synapses

GABA analogue binding to -2- subunit of voltage Ca^{2+} channels

Reduces Ca^{2+} in ux into neurons

Inactive at GABA receptors

Monitoring

No speci c plasma monitoring available

Monitor for weight gain

Side e ects

CNS: blurred vision, confusion, dizziness, memory impairment, suicidal risk

Constipation, nausea, peripheral oedema

Weight gain

Rarely: low platelets, PR prolongation, creatinine kinase (CK) release

Pharmacokinetics

Absorption: absorbed more rapidly than gabapentin (3-fold increase). It occurs throughout the small intestine, via multiple transporter mechanisms, and the ascending colon (unlike

gabapentin). Bioavailability >90%. First-order kinetics—concentration is linearly dose-dependent. Peak concentration 1 hour after administration

Distribution: no protein binding

Metabolism: negligible (<2%)

Excretion: primarily eliminated through renal excretion (98%) as unchanged compound in the urine

t1/2: 5–7 hours

E ectively cleared through renal haemodialysis in patients with end-stage renal failure

Pregabalin is excreted mainly unchanged by renal mechanism. Important to reduce the dose in renal impairment:

Maximum 300 mg/day if eGFR 30–60 mL/min

Maximum 150 mg/day if eGFR 15–30 mL/min

Maximum 75 mg/day if eGFR <15 mL/min

Interactions

Minimal interactions

Caution with other sedative and anxiolytic drugs

Special circumstances

Pregnancy: avoid due to major risk of neural tube defects

Breastfeeding: limited data; avoid for pain management; if used, then monitor infant for sedation. Infants can have withdrawal when breastfeeding stopped

Children: 2.5–15 mg/kg has been tried. Increased emotional and behavioural S/Es

Elderly: increased cognitive S/Es, hence lower doses to be used. Care in renal impairment

Additional information

Withdrawal e ect experienced by many patients; care needs to be taken to taper down pregabalin and gabapentin appropriately

Very few studies available for prophylaxis of chronic pain; however, results from one RCT showed promise in the reduction of incidence of chronic knee pain after total knee arthroplasty with use of pregabalin preoperatively up to 14 days after surgery

Also improves mood disturbance and sleep in PHN su erers, while also e ective in helping with central pain, sleep, and anxiety in spinal cord injury (SCI) patients

Easier to titrate, compared to gabapentin

Pregabalin 50 mg equivalent to gabapentin 300 mg

Cost

Great variability in cost between manufacturers

25 mg (56 capsules) = £2.16 (monthly supply)

300 mg (56 tablets) = £4.86 (monthly supply)

Oral solution: 20 mg/mL in 500 mL bottle: £75 (= 150 mg twice daily for 1 month)

Further reading

1. Gajraj N. Pregabalin: its pharmacology and use in pain management. Acute Pain 2008;10(1):51–2
2. Bockbrader H, Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet 2010;49(10):661–9

9.5 Carbamazepine

Class of drugs

Iminostilbene derivative, related to tricyclics

Indications

Trigeminal neuralgia— rst-line treatment (NNT 1.4–1.9)

Neuropathic pain (NNT 1.6–2.5)

Epilepsy: generalized tonic–clonic seizures and temporal lobe speci cally

Contraindications/caution

Bone marrow dysfunction, tricyclic hypersensitivity, syndrome of inappropriate antidiuretic hormone (SIADH), porphyria, depression, atrioventricular block, along with MAOIs

Dose

Recommendations are to start with modi ed release at low dose (100 mg) every 8–12 hours, with breakthrough dose of shorter-acting 100 mg preparation every 4 hours, maximum 1600 mg/day. Determining dose of longer-acting drug based on S/Es and therapeutic e ects

Expect dosing at around 400–1200 mg/day

Mechanism of action

Blockade of voltage-gated Na^+ channels in CNS and peripheral nervous system through speci c pore binding

Dose-dependent blockade reduces neuronal cell excitability, hence preventing ring of APs

Possible involvement of $GABA_A$ synaptic inhibition

Some evidence of serotonin reuptake inhibition and enhanced serotonin release

Inhibits glutamine release

Side e ects

CNS—dizziness, blurred vision, sedation, confusion

GI—nausea and vomiting, diarrhoea

Blood dyscrasia—leucopenia, thrombocytopenia, haemolysis

CVS—depressed atrioventricular conduction

Skin reactions—urticarial rashes

SIADH and hyponatraemia

Rarely—agranulocytosis, Stevens–Johnson syndrome (SJS), psychosis

Hepatotoxicity, cardiac arrhythmias

Higher dosing (>1000 mg/day)—can develop cerebellar symptoms (incoordination and ataxia) and cerebellar atrophy

Pharmacokinetics

Absorption: 100% bioavailability after oral administration

Distribution: 80–90% protein-bound

Metabolism: oxidation in the liver to the active metabolite epoxide; can induce its own metabolism with long-term use

Excretion: initial t1/2 25–65 hours, reduces to 12 hours after maintenance use. Clearance (3.59 L/min) is often consistent and not associated with body weight, age, or size

Interactions

Liver enzyme inducer—can enhance drug metabolism and hence reduce e cacy of other drugs, particularly oral contraceptive pills

Higher doses needed in patients taking concurrent phenytoin (approximately 25% higher)

Carbamazepine's plasma concentration can be reduced by other inducers, e.g. phenytoin, rifampicin, cisplatin, barbiturates, theophylline/aminophylline. Consider increasing the dose if needed

Reduces anticoagulant property of warfarin (OXC preferable)

Special circumstances

Pregnancy: higher incidence of neural tube defects; therefore, avoid in pregnancy where possible

Breastfeeding: can use in breastfeeding if bene ts outweigh risks, but consider close monitoring

Additional information

Less well tolerated, compared to other anticonvulsant drugs (number needed to harm (NNH) 2.6)

Avoid if known HLA-B1502 (increased risk of SJS)

Aim for plasma concentrations of 4–12 micromoles/L (measure after 2 weeks of treatment), as risk of unwanted e ects signi cantly increases beyond this range

Will require monitoring for liver function tests (LFTs), renal function, FBC, Na^+, TFT, and HLA-B1502

Not cleared by haemodialysis

Cost

100 mg (28 tablets): £2.07–4.50 (manufacturer-dependent)

400 mg (56 tablets): £5.05

Monthly cost for a dose of 400–1200 mg/day: approximately £2.50–7.50

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Sasada M, Smith S. Drugs in Anaesthesia and Intensive Care. 1st edition, 2003. Oxford: Oxford University Press
3. Jacob S, Nair A. An updated overview on therapeutic drug monitoring of recent antiepileptic drugs. Drugs R D 2016;16(4):303–16

9.6 Oxcarbazepine

Class of drugs

Ketoanalogue of carbamazepine

Indications

Trigeminal neuralgia—NNT comparable to that of carbamazepine

Use if increasing S/Es with carbamazepine at increasing doses

Contraindications/caution

Sensitivity to tricyclics or carbamazepine, severe renal impairment, hyponatraemia, depression

Dose

Dosing 300 mg twice daily, increasing up to 1200 mg twice daily (no more than 600 mg/week increments); maximum: 2400 mg/day

Carbamazepine:OXC = 1:1.5

Mode of action

Similar action to that of carbamazepine

Totally absorbed and partially metabolized to the active hydroxyl metabolite compound monohydroxy derivative (MHD), which also inhibits K^+ channels, as well as Na^+ channels

Monitoring

Monitor for hyponatraemia, and monitor liver function for acute toxicity

Side effects

Similar to carbamazepine

Pharmacokinetics

Absorption: 70% bioavailability

Distribution: 40% protein-bound

Metabolism: by the liver to MHD metabolite (pharmacokinetics are complex for OXC)

Excretion: t1/2 of active MHD is 9 hours (only 2 hours for OXC itself)

Little effect on CYP450 system

Interactions

OXC is itself a potent liver enzyme inhibitor, but its concentration can be reduced by other inducers and it may increase the plasma concentration of other drugs

Special circumstances

Pregnancy: insufficient data available to determine safety

Breastfeeding: can be used, but monitoring for drowsiness is advised by manufacturers

Additional information

Better S/E profile than that of carbamazepine

Avoid with tricyclic compounds and MAOIs

Reduces effectiveness of contraceptive pill

May exacerbate narrow angle closure glaucoma

MHD of OXC is the active metabolite, which is absorbed from the proximal small bowel. May need to consider alternatives in cases of duodenal resection

30% cross-allergy with carbamazepine

Better than carbamazepine when anticoagulated with warfarin

Cost

300 mg (50 tablets) = £7.09
600 mg (50 tablets) = £38.71
Monthly supply for 300–1200 mg twice daily: £8.50–93.00
Oral suspension 60 mg/mL in 250 mL bottle: £49 (monthly supply for 500 mg/day)

Further reading

1. Sasada M, Smith S. Drugs in Anaesthesia and Intensive Care. 1st edition, 2003. Oxford: Oxford University Press
2. Flesch G. Overview of the clinical pharmacokinetics of oxcarbazepine. Clin Drug Investig 2004;24(4):185–203
3. Zhou M, Chen N, He L, et al. Oxcarbazepine for neuropathic pain. Cochrane Database Syst Rev 2013;3:CD007963

9.7 Sodium valproate

Class of drugs

Valproate and valproic acid are organic carboxylic acid hydrocarbons

Indications

Epilepsy, neuropathic pain, migraine prophylaxis, bipolar disorder, schizophrenia, dopamine dysregulation syndrome

Contraindications/caution

Pregnancy
Pre-existing liver dysfunction
Metabolic and mitochondrial disorders
Acute porphyrias
Systemic lupus erythematosus (SLE)

Dose

Initial dose 600 mg daily in two divided doses. Increase gradually by 150–300 mg every 3–4 days. Maintenance 1–2 g/day; maximum of 2.5 g/day in divided doses

Mode of action

Stabilizes inactive Na^+ channels
Increases brain GABA levels
Reduces nerve cell excitability

Monitoring

Therapeutic range 20–100 mg/L

Side e ects

Common S/Es include weakness, nausea, vomiting, sedation, and dizziness

Less commonly, bleeding, thrombocytopenia, encephalopathy, suicidal ideation, and hypothermia

Pharmacokinetics

Absorption: 100% bioavailability

Distribution: highly protein-bound (90%)

Metabolism: liver glucuronidation (30–50%)

Excretion: 3% unchanged in the urine

t1/2: between 8 and 20 hours

Valproic acid is a potent androgen antagonist and an aromatase inhibitor. Lowers oestrogen concentrations, leading to lower fertility. Can increase gonad androgen biosynthesis via inhibition of histone deacetylases

Higher rates of menstrual disorder and polycystic ovary syndrome

Interactions

Multiple interactions mainly via inhibition of CYP2C9, glucuronyl transferase, and epoxide hydrolase

Displacement of other protein-bound drugs

Inhibitors of cytochrome P450 (e.g. cimetidine) will increase valproate levels

Inducers of cytochrome P450 (phenytoin, carbamazepine, barbiturates, and rifampicin) will reduce valproate levels

Other anticonvulsants—reduced clearance of both drugs

Warfarin—increased concentration and prolonged bleeding time

Special circumstances

Pregnancy: not recommended as it causes birth defects, neural tube defects, lower intelligence quotient (IQ), and autism

Breastfeeding: theoretical risk, but no proven adverse reactions. Can be used with breastfeeding if bene ts outweigh risks, but consider close monitoring

Children: liver dysfunction, especially in children aged under 3 years with metabolic or degenerative disorders

Elderly: increased sedation in patients with dementia

Additional information

Evidence for e ectiveness in diabetic neuropathy is weak. A Cochrane review in 2011 reported insu cient evidence to use as rst-line agent for neuropathic pain

Lack of data, and RCT results for other neuropathic types of pain are sketchy at best

For neuropathic pain, its use is limited by dose-dependent S/Es; evidence remains poor for use in chronic neuropathic conditions

Sodium valproate shows e ectiveness in an open trial for treatment of cluster headaches and has the bene t of a single daily dose

A meta-analysis showed NNT of 5 for 50% reduction in migraine when used as prophylaxis

Cost

200 mg (30 tablets): £2.77
300 mg (30 tablets): £5.24
500 mg (30 tablets): £8.73
Monthly supply (600–2500 mg/day): approximately £11–44
Oral solution 200 mg/5 mL in 300 mL bottle: £7.78 (for 600–2500 mg/day monthly supply: £12–50)

Further reading

1. Gill D, Derry S, Wi en PJ, Moore RA. Valproic acid and sodium valproate for neuropathic pain and bromyalgia in adults. Cochrane Database Syst Rev 2011;2011(10):CD009183. Published 2011 Oct 5. Doi:10.1002/14651858. CD009183.pub2
2. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev 2013 Jun 24;(6):CD010611. Doi: 10.1002/14651858.CD010611. PMID: 23797677

9.8 Phenytoin

Class of drugs

Hydantoin derivative (glycolylurea)

Indications

Epilepsy (tonic–clonic and focal) and post-surgery seizure prophylaxis
Status epilepticus
Malignant ventricular arrhythmias
Digoxin toxicity
Neuropathic pain

Contraindications/caution

Pregnancy
Breastfeeding
Acute porphyrias
Second-degree or complete heart block
Sinus bradycardia
Sinoatrial (SA) node block

Dose

Starting dose for adults: 3–4 mg/kg daily or 150–300 mg once or twice daily
Usual maintenance 200–500 mg daily, to be taken preferably with or after food

Mode of action

Membrane stabilization by binding to Na^+ channels and slowing inward Na^+ and Ca^{2+} ux during depolarization, and delaying outward K^+ ux

Blockade of further AP generation
Enhances action of GABA
May counteract allodynia and hyperalgesia associated with neuropathic pain

Monitoring

Narrow therapeutic window
Target 10–20 mg/L of total plasma phenytoin
Consider free phenytoin levels in reduced protein-binding states

Side e ects

Common—nausea, vomiting, incoordination, appetite loss, acne, hirsutism, gum hypertrophy
CVS—hypotension, complete heart block, arrhythmias
CNS—nystagmus, ataxia, tremor, cerebellar atrophy, peripheral neuropathy
Blood dyscrasias—megaloblastic anaemia, folate de ciency
Teratogenicity, carcinogenesis
Skin—SJS, itching, toxic epidermal necrolysis (TEN)
Drug-induced lupus, immunoglobulin A (IgA) de ciency
Suicidal thoughts
Reduced bone density

Pharmacokinetics

Absorption: bioavailability 85–95% after oral dose
Distribution: highly protein-bound (90–90%)
Metabolism: mainly by CYP450 system to 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH). It follows mixed-order elimination— rst-order kinetics initially, and then rapid saturation of enzymes leads to achievement of zero-order kinetics just above the therapeutic level, hence a narrow therapeutic margin. Rapid accumulation with minor dose increments
Excretion: 70–80% excreted in the urine and <5% unchanged

Interactions

Potent inducer of liver enzymes—causes possible widespread interactions
Metronidazole and isoniazid precipitate phenytoin toxicity
Reduces e ectiveness of warfarin, pethidine, and BZDs
Highly protein-bound—hence, protein displacement leads to high concentrations of free drugs in some cases
To be used cautiously with all antiarrhythmics due to risk of bradycardia
Not cleared by haemodialysis

Special circumstances

Pregnancy: teratogenic drug—therefore, avoid use
Breastfeeding: can be used with breastfeeding if bene ts outweigh risks, but consider close monitoring
Children: avoid using for pain
Elderly: higher risk of S/Es due to di erence in kinetics. If prescribed, use smaller doses

Additional information

Phenytoin is used very infrequently for pain

A Cochrane review in 2012 to nd evidence of its use in chronic pain could not nd any good-quality RCT with robust inclusion criteria and a conclusion of 'no evidence of su cient quality' was made by the authors

Cost

100 mg (28 tablets) = £10.07
300 mg (28 capsules) = £9.11
Monthly supply for 200–500 mg daily: £20–30
Oral solution 6 mg/mL in 500 mL bottle: £4.27
Solution for injection 250 mg/5 mL vial= £48.79

Further reading

1. McCleane GJ. Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study. Anesth Analg 1999;89:985–8
2. Birse F, Derry S, Moore RA. Phenytoin for neuropathic pain and bromyalgia in adults. Cochrane Database Syst Rev 2012 May 16;2012(5):CD009485. Doi: 10.1002/14651858.CD009485.pub2. PMID:22592741; PMCID: PMC6481697

9.9 Lamotrigine

Class of drugs

Phenyltriazine *derivative*

Indications

Migraines
Cluster headaches
Bipolar disorder
Focal and generalized seizures

Contraindications/caution

Known sensitivity
Use cautiously in patients with anaemia and generalized blood dyscrasia

Dose

Start at 25 mg once daily, alternate days for 14 days, then daily for 14 days, increased to 50 mg once daily for a further 14 days. Increase up to 100 mg every 7–14 days, in steps
Maintenance 100–200 mg daily in 1–2 divided doses, increased if necessary, up to 500 mg daily
If restarting after 5 days' interval, the dose should be titrated again
NNT = 4

Mode of action

Triazine derivative inhibiting voltage-gated Na^+ channels, causing hyperpolarization of neuronal cell membrane and preventing the release of certain excitatory amino acids—of note, glutamate
Also inhibits 5-HT receptors and L-, N-, and P-type Ca^{2+} channels

Monitoring

No special plasma monitoring available

Side e ects

There have been reports of idiosyncratic skin reactions like SJS and TEN. Other non-speci c rashes have been reported. An allergic reaction risk is related to the initial concentration of lamotrigine in plasma; hence, low-dose initiation and slow uptitration are recommended

Well tolerated overall, with S/Es similar to those of gabapentin such as somnolence and dizziness

CNS—blurred vision, aggression, agitation, ataxia, diplopia, dizziness, drowsiness, headache, insomnia, nausea, nystagmus, tremor

MSK—arthralgia, back pain

GI—diarrhoea, dry mouth, nausea, vomiting

Skin—rash

Pharmacokinetics

Absorption: 98% bioavailability after oral dose, rst-order kinetics

Distribution: 55% protein-bound

Metabolism: via glucuronic acid conjugation in the liver to inactive metabolites

Excretion: elimination t1/2 29 hours

Interactions

Liver enzyme inducers can shorten the t1/2 of lamotrigine, so dose increases may be required

Oestrogen-containing drugs reduce serum levels of lamotrigine, so women on such medications may require a higher dose

Interaction with valproate enhances the action of both drugs and potentiates drug S/Es. Rare cases of neuroleptic malignant syndrome have also been reported

Special circumstances

Pregnancy: not recommended during rst trimester as increased risk of cleft lip and palate

Breastfeeding: expressed in breast milk; manufacturers recommend to avoid if breastfeeding

Children: rash is the most common S/E

Additional information

A Cochrane review in 2013 revealed no convincing evidence for the use of lamotrigine in chronic pain; in fact, trials showed a higher rate of unwanted S/Es, when compared to placebo

Cost

25 mg (56 tablets): £1.70

100 mg (56 tablets): £3.12

200 mg (56 tablets): £3.92

Monthly supply for 200–500 mg/day: £2–6

Further reading

1. Lynch M, Watson C. The pharmacotherapy of chronic pain: a review. Pain Res Manag 2006;11(1):11–38
2. Wi en PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. Cochrane Database of Systematic reviews 2011, Issue 2. Art. No.: CD006044. DOI: 10.1002/14651858.CD006044.pub3

9.10 Topiramate

Class of drugs

Sulfamate-substituted monosaccharide compound, unlike any other anticonvulsants in use

Indications

Epilepsy, weight loss, migraine prophylaxis, bipolar disorder, borderline personality disorder, alcoholism

Cluster headaches

Migraines

Contraindications/cautions

Acute porphyria

Kidney stones—topiramate changes urine pH, hence an increased risk of causing renal stones

Acroparaesthesia due to inhibition of carbonic anhydrase

Dose

Start at 25 mg once daily for 1 week at night and then can be increased by 25–50 mg every week. Usual dose of 50–100 mg/day in two divided doses

Maximum 200 mg daily

Mode of action

Modulates voltage-gated Na^+ channels and voltage-gated Ca^{2+} channels

Inhibits carbonic anhydrase

Enhances action of GABA

Blocks neurotransmission and prevents the release of excitatory amino acids—of note, glutamate

Monitoring

Serum/plasma level can be monitored for epilepsy or overdose

Levels usually <10 mg/L

Side e ects

Common S/Es include weight loss, nausea, fatigue, and cognitive dysfunction

Di culty with word nding is speci c to topiramate and seen in one-third of patients

Use limited by dose-dependent S/Es

Pharmacokinetics

Absorption: rapid absorption from the gut, 80% bioavailability

Distribution: 13–17% protein-bound

Metabolism: hydroxylation, hydrolysis, and glucuronidation
Excretion: 70% excreted unchanged in the urine
t1/2: 19–25 hours

Interactions

Topiramate can alter the concentration of other anticonvulsant drugs. Use cautiously in epileptic patients using phenytoin, valproate, carbamazepine, lithium, barbiturates, and metformin
Hyperammonaemia and CNS toxicity reported when combined with valproic acid

Special circumstances

Pregnancy: avoid as proven link with cleft palate when taken in rst trimester
Breastfeeding: avoid, as per manufacturer, as small amounts in breast milk
Children: unlicensed use for migraine prophylaxis; can cause vertigo, fever, and vomiting
Elderly: increased cognitive impairment and risk of falling

Additional information

An RCT in 2006 showed positive changes in pain sensitivity, subjective disability, health-related QoL, and weight loss when used for chronic lower back pain
Used in neuropathic pain, but limited by dose-dependent S/Es, while evidence remains poor for use in chronic neuropathic conditions
Used successfully in cases of trigeminal neuralgia in MS patients, although evidence for its use in non-MS subjects is less dramatic
Used in migraine prophylaxis as can cause cerebral vasodilatation
Has undergone trials for other conditions, including PTSD, infantile spasms, periventricular leucomalacia, and hypoxic–ischaemic injury
Promotes weight loss in overweight people

Cost

25 mg (60 tablets): £9.50
50 mg (60 tablets): £9.50
Monthly supply for 50–100 mg: £9.50
Oral suspension 10 mg/mL in 150 mL bottle: £129 (monthly: £129–200)

Further reading

1. Chong M, Libretto S. The rationale and use of topiramate for treating neuropathic pain. Clin J Pain 2003;19(1):59–68
2. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev 2013 Jun 24;2013(6):CD10610. Doi: 10.1002/14654858.CD010610. PMID:23797676; PMCID: PMC7388931
3. Zvartau-Hind M, Din M, Gilani A, et al. Topiramate relieves refractory trigeminal neuralgia in MS patients. Neurology 2000;55(10):1587–8

CHAPTER 10

Antidepressants

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10.1 Overview of antidepressants

Introduction

Prevalence of chronic pain and mood disorders is common and varies, depending on the clinical setting studied (around 50% in chronic pain clinics)

Simultaneous treatment of chronic pain and mood disorders is needed to achieve good outcomes

Antidepressants can be used as part of a multidisciplinary approach addressing the physical, psychological (psychiatric or psychological), and social (work, litigation, social support network) contributors to pain, disability, and distress

Consider the use of non-pharmacological strategies to improve mood and pain. These can include training in relaxation, mindfulness, and other forms of psychotherapy such as acceptance and commitment therapy (ACT), cognitive behavioural therapy (CBT), dialectical behaviour therapy (DBT), supportive therapies, family/couples/marital therapies, and psychodynamic therapies

Classi cation

MAOIs: phenelzine, isocarboxazid

TCAs: amitriptyline, nortriptyline, imipramine

SSRIs: citalopram, sertraline, uoxetine

SNRIs: duloxetine, venlafaxine, desvenlafaxine, milnacipran

Tetracyclic/unicyclic antidepressants: mirtazapine

Serotonin antagonist and reuptake inhibitors: trazadone

Melatonergic and serotonin reuptake inhibitors: valdoxan

Mode of action

Improve mood and pain, and vice versa. The exact mode of action is unknown, but some mechanisms of action may be through:

Restoring the imbalance or de ciency of key NTs (serotonin, noradrenaline, dopamine, glutamate, GABA) widely distributed throughout the brain

Potentiating descending inhibitory pathways at the spinal level (e.g. acting on opioid receptors in the DH) and other areas of the CNS such as PAG

Indications

Treatment of anxiety and depressive disorders

Symptomatic treatment of common presentations such as anxiety, insomnia, and irritability

Direct treatment of neuropathic pain:

General consensus is that TCAs are the most e ective antidepressants but have the most adverse e ects

Most of the evidence is from diabetic neuropathy and PHN

Antidepressants can be used in acute neuropathic pain, based on experience from chronic neuropathic pain

Analgesic e cacy—pharmacotherapy for neuropathic pain

First line (TCA or SNRI or gabapentinoids):

TCA (amitriptyline 25–150 mg): moderate evidence, moderate e ect size (NNT 3.6), low to moderate tolerability/safety (NNH 13.4)

SNRI (duloxetine 60–120 mg): high evidence, moderate e ect size (NNT 6.4), moderate tolerability/safety (NNH 11.8)

Gabapentinoids (pregabalin 150–600 mg or gabapentin 1200–3600 mg): high evidence, moderate e ect size, tolerability/safety (high for gabapentin and moderate for pregabalin)

Second line: tramadol or capsaicin patch 8% or topical lidocaine

Third line: strong opioids or botulinum toxin type A (BTX-A)

Administration and dose

Given by the oral route

To be considered in patients with neuropathic pain, particularly if associated with symptoms of insomnia (TCA) and low mood and/or anxiety (TCA/SNRI)

Initiation at low dose (taking into account risk factors for toxicity) and titrated according to e ect. Titrations of di erent antidepressants is a ected by the pharmacokinetics and inter-individual variations in drug handling

The lowest e ective dose should be maintained

Should intolerable S/Es occur, the patient should be stepped back down to the highest dose tolerated

Caution and use lower doses in the elderly and in renal and hepatic impairment due to decreased excretion

When started, possible increased risk of suicide-related events in those with a depressive/psychiatric condition. An adequate risk assessment for suicide needs to be done before commencing antidepressants, and appropriate ongoing support is required

Beware that when antidepressants are weaned, potentially there can be a deterioration in the mental state and increased suicidal ideation

Beware the withdrawal phenomenon when discontinuing particularly SSRIs and SNRIs. Titrate the dose down slowly (at least a minimum of every 2 weeks) if the dose has been high or for a prolonged duration. Monitor closely for withdrawal symptoms such as nausea, vomiting, dizziness, agitation, anxiety, headache, and other symptoms

Discuss with patients and other clinicians discontinuing antidepressants if these are no longer needed as they cause S/Es. When and how to do this is di erent patient by patient

Additional information

Generally, avoid using antidepressants for pain management in pregnancy, breastfeeding, and children. If the bene ts outweigh the risks, use the safest and most e ective antidepressant

There is con icting evidence of whether combining antidepressants with other analgesics for pain management is useful

Further reading

1. Hooten M. Chronic pain and depression. In: Wilson P, Jensen T, Watson P, Haythornthwaite JA (eds). Clinical Pain Management: Chronic Pain. 2008; pp. 241–53. London: Hodder
2. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73

10.2 Tricyclic antidepressants

Indications

Depression

Neuropathic pain:

- E ective in diabetic neuropathy, PHN, HIV sensory neuropathy, central post-stroke pain, post-mastectomy pain, trigeminal neuralgia
- E cacy NNT 2–3 and NNH 13.4
- Sedative e ects can be useful in patients with sleep disturbances

Prophylaxis of migraine

Contraindications

Acute porphyrias; arrhythmias; manic phase of bipolar disorder; heart block; recent MI, severe liver disease (relative), simultaneous use of other medications such as tramadol, warfarin, SSRIs, MAOIs

Dose

Starting dose 10–25 mg nocte, gradually increased if necessary

Neuropathic pain: 10–50 mg daily

Depression or migraine prophylaxis: maximum daily dose 150 mg

Mode of action

Reuptake inhibition of serotonin and noradrenaline (via the metabolite nortriptyline)

Receptor blockade: muscarinic cholinergic, -1 adrenergic, histamine H1, NMDA

Ion channel blockade: Na^+, Ca^{2+}

Monitoring

Patients should be monitored closely for changes in behaviour, clinical worsening of the mental state, and suicidal tendencies; this should be done during the initial 1–2 months of therapy and dosage adjustments

Side e ects

Common: dry mouth, constipation, fatigue, drowsiness, dizziness, postural hypotension, blurred vision, urinary hesitancy, confusion (elderly), risk of falls

Rare: dysarthria, sexual dysfunction, extrapyramidal symptoms, tremor, oedema, cardiac conduction defects

Very rare: neuroleptic malignant syndrome, precipitation of angle closure glaucoma

Frequency unknown: arrhythmias, paraesthesiae, rash, taste disturbance, nausea, vivid dreams

Relevant pharmacokinetics

Absorption/distribution: oral bioavailability 45%, peak serum level 4 hours, 95% protein-bound, large Vd

Metabolism: signi cant variability in patients due to genetic variability. Amitriptyline undergoes N-demethylation into its primary active metabolite nortriptyline by hepatic CYP2C19. This secondary amine is hydroxylated by CYP2D6 and conjugated to glucuronide and sulphates

Excretion: mostly as inactive conjugates in the urine, minimal amounts in faeces. Elimination t1/2: 13–36 hours

Relevant pharmacodynamics

CVS: postural hypotension, sinus tachycardia, dysrhythmia, increase in AV conduction time, prolonged PR and QT intervals

CNS: sedation, fatigue, respiratory depression in toxic doses

Interactions

SSRI: increased adverse e ects

Adrenaline/noradrenaline/phenylephrine: increased e ects

Alcohol: increased CNS depression

Antiarrhythmic drugs: increased risk of ventricular arrhythmias

Antipsychotics: increased sedation, additive anticholinergic e ects

Barbiturates: decreased activity

Clonidine: antihypertensive e ects reduced or abolished

Lithium: risk of neurotoxicity

MAOIs: mutual enhancement, hypertension, hyperpyrexia, convulsions, and coma

Tramadol: increased risk of seizures and serotonergic syndrome

Special circumstances

Renal impairment: use with caution, but normally dose reductions are not needed

Hepatic impairment: dose reduction in severe liver impairment

Pregnancy: use with caution; consider if bene ts outweigh risks

Lactation: the amount secreted into breast milk is too small to be harmful

Elderly: susceptible to many of the S/Es; low doses, with close monitoring

Driving: drowsiness may a ect the performance of skilled tasks

Additional information

Nortriptyline (5–50 mg) can sometimes be more e ective, with fewer S/Es, than amitriptyline

TCAs can attenuate the cardiovascular e ects of adrenaline during general anaesthesia

Overdosage: associated with a relatively high rate of fatality

Withdrawal symptoms: the risk is increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks

Cost

Amitriptyline 10 mg (28 tablets): £0.89
Amitriptyline 25 mg (28 tablets): £0.76
Amitriptyline 50 mg (28 tablets): £2.02
Nortriptyline 10 mg (28 tablets): £1.85
Nortriptyline 25 mg (28 tablets): £2.27
Nortriptyline 50 mg (30 tablets): £21.13
Prices for oral solutions are signi cantly higher than for tablet form (10 mg/mL for 250 mL bottle: £246; 1-month supply for 10–50 mg/day: £10–50)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73
3. Sindrup SH, Otto M, Finnerup NB, et al. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol 2005;96:399–409

10.3 Serotonin and noradrenaline reuptake inhibitors

Indications

Neuropathic pain
Major depressive disorder
Anxiety disorder

Mechanism of action

The exact analgesic mechanisms of action of SNRIs is unknown but may be through blockade of reuptake of serotonin and/or noradrenaline
Venlafaxine has a dose-related e ect:
- Low dose: serotonin blocked
- Medium dose: serotonin and noradrenaline blocked
- High dose: serotonin, noradrenaline, and dopamine blocked

Analgesic e cacy

SNRIs and TCAs are more e ective than SSRIs for the management of neuropathic pain
Duloxetine: NNT 5.8, NNH (minor) 11.8, and NNH (major) 17
Venlafaxine: NNT 6.4, NNH (minor) 9.6, and NNH (major) 16.2
Evidence indicates that duloxetine (60–120 mg daily) provides:
- Analgesia for diabetic neuropathy and other presentations of neuropathic pain
- Analgesia and improved QoL in bromyalgia, but no e ect on sleep or fatigue

In diabetic polyneuropathy, venlafaxine and duloxetine are superior to TCAs with regard to both analgesia and S/Es

Routes of administration and dosing

Duloxetine: commence at 30 mg, increased to 60 mg daily, maximum 120 mg daily

Venlafaxine: 75 mg daily in two divided doses, maximum 375 mg daily. Dose-related e ect (analgesic at higher doses)

Renal impairment (creatinine clearance <30 mL/min): duloxetine and venlafaxine dose reduction

Liver impairment: duloxetine should not be used; venlafaxine dose reduction

Pharmacokinetics

Duloxetine:

- Absorption: bioavailability 50%
- Distribution: 96% protein-bound
- Metabolism: hepatic via cytochrome P450 (especially CYP1A2 and CYP2D); large inter-subject variability in response
- Excretion: elimination t1/2: 8–17 hours, mainly in the urine

Venlafaxine:

- Absorption: bioavailability 92%
- Distribution: 60% protein-bound, Vd 5 L/kg
- Metabolism: hepatic via cytochrome P450 to weakly active metabolites
- Excretion: renal

Adverse e ects

Cardiovascular: prolongation of QT interval, torsades de pointes

GI: duloxetine can commonly cause nausea and vomiting

Haematological: increased bleeding risk from blocking serotonin reuptake into platelets

Metabolic: hyponatraemia

Nervous system:

- Worsening of depressive symptoms/increase suicide-related event risk, mostly when initiated
- Paradoxical anxiety, insomnia, delirium, akathisia, seizures, headache, dizziness
- Serotonin syndrome—avoid serotonergic medicines, including triptans and tramadol

Skin/MSK: rash, myalgia, arthralgia

Contraindications

Patients on MAOIs—risk of serotonin-type syndrome

Prolonged QT syndrome or if taking other drugs that prolong the QT interval

Caution in diabetics—may alter glucose control

Caution in epileptics—may lower seizure threshold

Caution in patients with bleeding abnormalities or co-administered anticoagulants

May precipitate closed angle glaucoma in susceptible patients

Additional information

Pregnancy:

- Duloxetine: caution recommended
- Venlafaxine: not recommended

Breastfeeding:

- Duloxetine, venlafaxine: not recommended

Children:

- Duloxetine, venlafaxine: avoid under 18 years of age

Desvenlafaxine (metabolite of venlafaxine) is sometimes better tolerated. Dose 50–200 mg daily
Milnacipran is a more recent selective SNRI licensed for bromyalgia and neuropathic pain (not in the UK). It has been found to provide pain relief to a minority of people

Cost

Duloxetine 30 mg capsules (28 pack): £22.40
Duloxetine 60 mg capsules (28 pack): £27.72
Venlafaxine 37.5 mg tablet (56 pack): £7.95
Venlafaxine 75 mg tablet (56 pack): £15.95

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10.4 Selective serotonin reuptake inhibitors

Indications

Major depressive disorder
Anxiety disorder
Neuropathic pain (poor evidence)

E cacy

SNRIs and TCAs are better analgesics than SSRIs in the management of neuropathic pain
SSRIs are safer in overdose than TCAs
E ective at targeting anxiety, depression, and arousal

Mechanism of action

The exact analgesic mechanism is unknown but may be through blockade of reuptake of serotonin with no, or minimal, e ect on noradrenaline
Citalopram is the most selective SSRI, with minimal e ect on noradrenaline, dopamine, and GABA uptake

Routes of administration and dosing

Citalopram: 20–40 mg PO daily
Sertraline: 50–200 mg PO daily
Fluoxetine: 20–60 mg PO daily

Pharmacokinetics

Citalopram:

- Absorption: bioavailability 80%
- Distribution: 80% protein-bound, Vd 12.3 L/kg
- Metabolism: hepatic via cytochrome P450 (especially CYP2C19, but also CYP3A4) to active metabolites with (weaker) SSRI activity. Displays linear kinetics, with steady state achieved in 1–2 weeks
- Excretion: elimination t1/2 1.5 days, 85% via the liver and 15% via the kidneys

Sertraline:

- Absorption: good oral bioavailability
- Distribution: 98% protein-bound
- Metabolism: hepatic via cytochrome P450 (mainly CYP3A4, CYP2C19, and CYP2B6)
- Excretion: elimination t1/2 26 hours, 50% via the liver and 50% via the kidneys

Fluoxetine:

- Absorption: good oral bioavailability
- Distribution: 95% protein-bound, Vd 20–40 L/kg
- Metabolism: hepatic via cytochrome P450 to active nor uoxetine
- Excretion: elimination t1/2 4–6 days for uoxetine and 4–16 days for nor uoxetine (hence persistence of the drug for 5–6 weeks after discontinuation)

Adverse e ects

Nervous system: worsening of depressive symptoms/increased suicide-related event risk, mostly when initiated. Paradoxical anxiety, insomnia, delirium, akathisia, seizures, headache, dizziness. Serotonin syndrome—avoid serotonergic medicines, including triptans and tramadol. Citalopram appears to have the least adverse e ects on the nervous system of the SSRIs

Cardiovascular: prolongation of QT interval, torsades de pointes. Interaction with linezolid (citalopram), causing severe hypertension

Metabolic: hyponatraemia

Haematological: increased bleeding risk from blocking serotonin reuptake into platelets

Skin/MSK: rash, myalgia, arthralgia

Contraindications

Patients on MAOIs—risk of serotonin-type syndrome

Prolonged QT syndrome or if taking other drugs that prolong the QT interval

Caution in diabetics—may alter glucose control

Caution in epileptics—may lower seizure threshold

Caution in patients with bleeding abnormalities or co-administered anticoagulants

May precipitate closed angle glaucoma in susceptible patients

Special considerations

Pregnancy

- Citalopram considered safe by manufacturer
- Sertraline and uoxetine: not recommended

Breastfeeding

- Citalopram and uoxetine: caution recommended
- Sertraline: not recommended

Children

Citalopram: avoid in those under 18 years of age

Sertraline only for treatment of obsessive–compulsive disorder (OCD)

Fluoxetine licensed in children over 8 years of age

Additional information

Agomelatine is a melatonin receptor agonist and a selective serotonin receptor antagonist which is sleep-enhancing, and can be used with other antidepressants (o -label). LFT monitoring is required (28 tablets cost £30)

Cost

Citalopram 10 mg tablets (28 pack): £0.90

Citalopram 40 mg tablets (28 pack): £1.46

Sertraline 50 mg tablets (28 pack): £4.50

Sertraline 100 mg tablets (28 pack): £7.99

Fluoxetine 20 mg capsules (30 pack): £1.15

Fluoxetine 40 mg capsules (30 pack): £1.80

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10.5 Mirtazapine

Indications

Moderate/major depression—particularly if the patient also has anorexia, weight loss, and insomnia

Contraindications

Hypersensitivity to mirtazapine

Concomitant use or within 2 weeks from cessation of MAOIs

Dose

Starting dose 15–30 mg/day; range is 15–45 mg/day

In elderly patients, the starting dose can be lower (7.5 mg)

Caution is required in moderate/severe liver and renal impairment as clearance is reduced

Lower doses used for depression and insomnia. At higher doses, there are less sedative e ects

Mode of action

Antagonist at pre-synaptic -2 adrenergic inhibitory receptors on both serotonin and noradrenaline pre-synaptic axons, resulting in an increased release of noradrenaline

Potent antagonist of 5-HT2 and 5-HT3 receptors. There is increased 5-HT1 activity due to selective enhancement of 5-HT1 receptors

Potent antagonist of histamine (H1) receptors, contributing to its sedative e ects

Moderate peripheral -1 adrenergic antagonist which can lead to orthostatic hypotension

Moderate antagonist at muscarinic receptors which may explain low anticholinergic S/Es

Its mechanism of action is not related to noradrenaline or serotonin reuptake blockade

At lower doses, it improves sleep as it has a higher a nity for histamine receptors. At higher doses, there is less sedating e ect because there is less antihistamine e ect and more noradrenergic transmission

Monitoring

Patients should be advised to report any fever, sore throat, stomatitis, or other signs of infection during treatment. Blood count should be performed and the drug stopped immediately if blood dyscrasia is suspected

Close monitoring is required when simultaneously used with serotonergic active substances

Side e ects

Common: sedation, dry mouth, weight gain, increased appetite, dizziness, fatigue

Less common: abnormal dreams, tremor, nausea, arthralgia

Rare: myoclonus, elevation of transaminase levels, bone marrow suppression, hyponatraemia, toxic epidermal necrolysis, Stevens-Johnson syndrome

Relevant pharmacokinetics/pharmacodynamics

Absorption: oral bioavailability 50%, reaching peak plasma levels after 2 hours of oral intake

Metabolism: demethylation and oxidation in the liver by cytochrome P450 enzymes. The demethyl metabolite is pharmacologically active

Elimination: via the urine (75%) and faeces (15%). Mean t1/2 is 20–40 hours. Steady state is reached after 304 days

Mirtazapine can cause minor/moderate cognitive impairment (e.g. impaired ability to drive, use machines, etc.)

Interactions

Warfarin: INR can be increased

MAOIs/serotonergic active substances: risk of serotonin-associated e ects

BZDs/antihistamines/opioids/antipsychotics: sedating properties may be enhanced

Alcohol: mirtazapine may worsen the CNS-depressant e ect of alcohol

CYP3A4 inducers (e.g. carbamazepine, phenytoin): can increase mirtazapine clearance by about 2-fold

CYP3A4 inhibitors (e.g. HIV protease inhibitors, azole antifungals): mirtazapine dose may have to be decreased due to reduced clearance

Paroxetine, amitriptyline, risperidone, or lithium: interaction studies did not indicate any relevant pharmacokinetic interactions

Special circumstances

Pregnancy: limited data do not indicate an increased risk of congenital malformations

Breastfeeding: excreted in breast milk only in very small amounts

Elderly: reduced clearance

Sometimes used as an antiemetic mostly in palliative care—evidence is controversial

Can be a good agent in underweight, depressed patients as can increase appetite and weight

Additional information

Some elderly patients can develop insomnia when mirtazapine is used at higher doses, such as 45 mg, due to increased noradrenaline concentrations. Some patients on higher doses take mirtazapine in the morning, aiming for less interference with sleep

Cost

Mirtazapine 15 mg tablets (28 pack): £1.22
Mirtazapine 30 mg tablets (28 pack): £1.09
Mirtazapine 45 mg tablets (28 pack): £1.32
Oral solution formulations are signi cantly more expensive

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CHAPTER 11

Neurolytic Agents

Hadi Bedran

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11.1 Ethyl alcohol

Indications

Alcohol is one of the main agents used for chemical neurolysis

Predominantly indicated in patients with a short life expectancy for management of cancer pain intractable to other modalities

Contraindications

Absolute: known allergy to ethyl alcohol

Relative: patients taking medications which inhibit alcohol dehydrogenase

Dose

Concentration used

Complete nerve destruction with concentrations of 100% or 95%

Partial nerve destruction with concentration of 50%

Analgesia has been achieved with concentration of 33%

Absolute alcohol is ideal for some peripheral nerve neurolytic blocks

Volumes used

Neuraxial blocks: normally 0.3–0.7 mL of alcohol per dermatome

Peripheral blocks need larger volumes, as alcohol rapidly spreads after it is injected from its site of action. In lumbar sympathetic/coeliac plexus, 10–20 mL of alcohol may be used bilaterally

Mode of action

Non-selective destruction of nerve tissue by precipitation of cell membrane proteins, extraction of lipid compounds, demyelination, and subsequent Wallerian degeneration

When alcohol is injected near the sympathetic chain, it destroys the ganglion cells and thus blocks all post-ganglionic fibres to all effector organs

Monitoring

Cardiac arrhythmias, hypotension, and skin and non-target tissue necrosis can occur

Patients on medications that inhibit alcohol dehydrogenase can develop disul ram-like reactions: ushing, vomiting, sweating, marked hypotension, and dizziness

Adverse e ects

Alcoholic neuropathy (common), hypoaesthesia, neuritis, dea erentation pain, motor de cit when mixed nerves are ablated, unintentional damage to non-targeted tissue and thrombosis if given IV

In neuro-axial blocks or blocks close to the spinal cord can get the adverse e ects already described and the following: bowel or urinary incontinence, neuralgias (e.g. genitofemoral neuralgia with lumbar sympathectomy), arterial vasospasm (spasm of the artery of Adamkiewicz can cause paraplegia)

Relevant pharmacokinetics/pharmacodynamics

Alcohol spreads rapidly from the injection site. When injected in the CSF, only 10% of the initial dose remains at the site of injection after 10 minutes and about 4% remains after 30 minutes

Between 90% and 98% of ethyl alcohol that enters the body is completely oxidized in the liver, principally by alcohol dehydrogenase

Denervation and pain relief accrue over a few days after injection, usually after 1 week

Interactions

Safe to be mixed with LAs, usually 1:1 ratio

Additional information

Alcohol is hypobaric in nature relative to the CSF. The position of the patient must be with the painful site in the uppermost and lateral decubitus position. After injection, the patient can be rolled anteriorly approximately 45° to place the dorsal (sensory) root uppermost

Alcoholic neuritis occurs frequently following thoracic paravertebral sympathetic block. This may be due to the close proximity of the sympathetic ganglia to the intercostal nerves. As a prophylactic measure, it is recommended to inject LA during insertion of the needle, at the site of injection before the alcohol is injected and on withdrawing the needle

Perineural injection of alcohol is followed immediately by severe burning pain along the nerve's distribution, which lasts about a minute, before giving way to a warm, numb sensation. Pain on injection may be diminished by prior injection of LA and using sedation during the procedure

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11.2 Phenol

Class of drug

Neurolytic drug made of carbolic acid, phenic acid, phenylic acid, phenyl hydroxide, hydroxybenzene, and oxybenzene

Can be prepared by the hospital pharmacy by dissolving 1 g of phenol in 15 mL of water (6.67%)

Indications

Phenol is one of the main agents used for chemical neurolysis. Predominantly indicated in palliative patients with a short life expectancy for management of intractable neuropathic pain refractory to other management modalities caused by:

- Cancer pain
- Persistent non-cancer pain
- Sympathetic-mediated pain intractable to other modalities

Used with caution for sclerotherapy of haemorrhoids (by injection)

Contraindications

Oily phenol injection: neonates or children

Allergy to any of the constituents of phenol

Dose

Sclerotherapy for haemorrhoids: 2–3 mL of phenol 5% in oil; maximum 10 mL

Neural/intrathecal: concentrations of 4–10% are typically used with sterile water or glycerol. In neuraxial blocks hyperbaric solutions (e.g. with glycerol) are preferred

Mode of action

Concentrations of <5% cause protein denaturation

Concentrations of >5% cause protein coagulation, non-speci c segmental demyelination, and Wallerian degeneration

Phenol has LA properties at lower concentrations

Monitoring

Signs of cardiac and CNS instability after every single use in neurolysis

Side e ects

Topical preparations: blanching, corrosion, pain, local ulceration, sterile abscess formation

Perineural/intrathecal injections: neuritis, dea erentation pain, unintentional damage to non-targeted tissue, motor de cit, hypoaesthesia

Relevant pharmacokinetics/pharmacodynamics

Hyperbaric relative to the CSF

Absorption: rapidly absorbed through the skin and into the lungs. After intrathecal injection, its concentration decreases rapidly to 30% of the original concentration in 60 seconds and to 0.1% within 15 minutes

Metabolism: conjugation to glucuronides and oxidation by liver enzymes

Clearance: the kidneys are the primary route of elimination

Therapeutic e ects: the process of neural degeneration takes about 14 days, and regeneration is completed in about 14 weeks

Adverse e ects

Toxic systemic doses of phenol (>8.5 g) are associated with convulsions, followed by CNS depression, and nally cardiovascular collapse

Chronic poisoning results in skin eruptions, GI symptoms, and renal toxicity

Clinical doses of between 1 and 10 mL of 1–10% solutions (up to 1000 mg) unlikely to cause serious toxicity

Unintentional damage to non-targeted tissue, neuralgias, dea erentation pain and thrombosis if given IV

In neuro-axial blocks or blocks close to the spinal cord can also develop bowel or urinary incontinence and arterial vasospasm (spasm of the artery of Adamkiewicz can cause paraplegia)

Interactions

None known

Additional information

Parental exposure to phenol and its related compounds is associated with spontaneous abortion

Phenol causes minimal discomfort when injected, whereas ethyl alcohol produces discomfort when administered

Less intense and shorter duration of block, when compared to alcohol

Further reading

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CHAPTER 12

Corticosteroids

Sadiq Bhayani, Bethany Fitzmaurice, and Ali a Tameem

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12.1 Overview of corticosteroids

Introduction

The adrenal cortex releases two classes of corticosteroids into circulation: GCs and mineralocorticoids

In this chapter, we focus on GCs and their synthetic analogues

Estimated human cortisol production = 5–10 mg/m²/day, equivalent to 20–30 mg/day of hydrocortisone and 5–7 mg/day of prednisolone

Anticipate HPA axis suppression with >30 mg/day of hydrocortisone/7.5 mg/day of prednisolone/0.75 mg of dexamethasone for >3 weeks, i.e. 'supraphysiological' doses

The British Pain Society/Faculty of Pain Medicine Consensus statement:

- Corticosteroid use for neuraxial interventions—ongoing debate due to reports of catastrophic neurological complications
- Su cient evidence to support continued use of corticosteroids in epidural injections for acute symptom relief, especially in the presence of acute radicular pain with disc herniation
- Limited evidence that particulate corticosteroid preparations have better e cacy than non-particulate preparations
- Particulate steroids must not be used for transforaminal cervical epidural injections
- Caution with interlaminar cervical epidurals and thoracic/lumbar/caudal routes
- Patients at increased risk if previous spinal surgery
- Small risk of neurotoxicity with inadvertent intrathecal injection due to preservatives (polyethylene glycol (PEG) in Depo-Medrone®). Many clinicians now prefer to use triamcinolone or dexamethasone
- Consent—use of epidural corticosteroids is outside the product licence and should be incorporated into the consent process

Pain-related indications

Not licensed in pain interventions for any route other than intra-articular

Acute pain

Acute herpes zoster, PHN prevention (remains speculative)

SLE (oral or local injection, e.g. enthesitis, tendonitis)

Polymyalgia rheumatica and giant cell arteritis—low-dose corticosteroids are the mainstay of treatment

Sickle cell crisis—a short course of high-dose methylprednisolone may decrease crisis duration

Post-operative pain—dexamethasone 0.1–0.2 mg/kg, opioid-sparing e ect

Acute painful in ammatory conditions, including CRPS, carpal tunnel syndrome, adhesive capsulitis, and painful cervical or lumbar radiculopathy

Chronic pain

Epidural for radicular pain, intra-articular, muscular (trigger point injection (TPI)), speci c nerves

Cluster headaches—transitional prophylactic treatment

PHN—intrathecal methylprednisolone: pain relief demonstrated

CRPS—PO prednisolone 10 mg three times daily demonstrated e cacy in acute CRPS (<13 weeks)

RA—to control pain or to bridge therapy of slower-acting agents

Temporomandibular dysfunction—topical or local injection

Cancer pain

Cerebral oedema headache (lower intracranial pressure (ICP))

Hepatic capsular stretch pain from liver metastases (reduce capsular in ammation)

Neuropathic pain and compressive symptoms (reduce perineural oedema); can reverse early nerve compression

Steroid enemas in treatment of tenesmus

Chemotherapy-induced arthropathy

Myeloma and associated pain: dexamethasone classed as chemotherapeutic agent

(See Table 12.1.1.)

Table 12.1.1 Classi cation of corticosteroids

Naturally occurring or synthetic	Particulate (poorly soluble) or non-particulate (soluble)	Preservative or preservative-free
Naturally occurring: Hydrocortisone (cortisol) Cortisone Corticosterone *Synthetic:* Prednisone Prednisolone Methylprednisolone Betamethasone Dexamethasone Triamcinolone	According to water solubility and aggregation characteristics '*Particulate*' = aggregates larger than red blood cells (6–8 micrometres) All synthetic corticosteroids are particulate, except dexamethasone (0.5 micrometres) and betamethasone	Multistate outbreak (2012) of fungal meningitis in patients receiving contaminated preservative-free methylprednisolone acetate (MPA) Majority include preservatives for sterility and enhanced shelf-life

Mode of action

Therapeutic e ects

Gene regulation:

Corticosteroids are gene-active hormones, targeting DNA molecules and inducing or repressing the synthesis of speci c messenger ribonucleic acid (mRNA) within a few minutes, although the physiological response may take hours to days to develop

Synthetic GCs have a higher a nity for the receptor, are less rapidly inactivated, and have little or no mineralocorticoid activity

Anti-in ammatory action:

Potent inhibition of cytokines, various in ammatory mediators, production and recruitment of in ammatory cells, and NO synthase

Inhibit plasma exudation at in ammatory sites and prevent intracellular water sequestration, thus preventing cell swelling and destruction

Mechanisms in pain relief:

Enhance pain-relieving e ects of LA by anti-in ammatory and direct analgesic e ects (inhibitory e ects on C- bre conduction)

Modulate pain pathways—decrease both peripheral and central neuronal hyperexcitability

Long-term pain reduction may be secondary to changes in gene expression

Injection into the epidural space allows a higher local concentration than systemic administration

Co-administration of LA interrupts sustained abnormal neural activity that perpetuates pain

Anti-swelling and anti-in ammatory e ects on nerve root and surrounding tissue, aiming to create su cient space and mobility of the nerve root to reduce or abolish pain

Metabolic e ects

Carbohydrates—stimulate hepatic gluconeogenesis, increase hepatic glycogen content, and inhibit insulin-mediated peripheral blood glucose uptake

Proteins—decrease anabolism, stimulate catabolism, and deplete the protein matrix of the vertebral column (trabecular bone), with minimal e ect on long bones (compact bone)

Lipids—permissive e ect on lipolytic hormones and fat redistribution

Immunosuppressive e ects

Modulate immune response, with leucocytosis but reduced antibody production, impair phagocytosis, reduce the number and function of circulating T-lymphocytes, and reduce (or decrease) the production in ammatory mediators

Vascular reactivity

Allow e cient response to circulating catecholamines, positive inotropy

Routes of administration and dosing

Little agreement about dose or type, with/without LA, volume, or frequency of injections

Dose and duration do not predict the extent of adrenal suppression as ACTH

If no bene t obtained after two injections, additional injections rarely e cacious

Repeated injections usually limited to three per year

Table 12.1.2 Corticosteroid potencies and dosing

Drug	Equivalent glucocorticoid dosing (mg)	Relative glucocorticoid activity	Relative mineralocorticoid activity	Duration of action (hours)	Plasma half-life (minutes)
Short-acting					
Cortisone	25	0.8	0.8	8–12	60
Hydrocortisone (cortisol)	20	1.0	1.0	8–12	90
Intermediate-acting					
Prednisone	5	4	0.6	24–36	60
Prednisolone	5	4	0.6	24–36	200
Methylprednisolone	4	5	0.5	24–36	180
Triamcinolone	4	5	0	24–36	300
Long-acting					
Dexamethasone	0.75	20–30	0	36–54	200
Betamethasone	0.6	20–30	0	36–54	200

(See Table 12.1.2.)

Note: $t_{1/2}$ does not represent the duration of action—this is best represented by the duration of ACTH suppression

Short-acting: advantageous when rapid clinical e ect desired, e.g. allergic reactions (highest mineralocorticoid potency)

Long-acting: prolonged anti-in ammatory e ects (weakest mineralocorticoid potency)

Side e ects and toxicity

Fluid retention, hyperglycaemia, elevated BP, mood changes, menstrual irregularities, gastritis, Cushing's syndrome, increased appetite, weight gain, infections, delayed wound healing, and acneiform eruptions. Short courses (<2–3 weeks) are safe, and S/Es rare

Local S/Es:

- Repeated intra-articular injections—severe joint destruction, bone necrosis, Charcot-like deformities
- Injection/leakage in skin—dermal and subdermal atrophy
- Intrathecal methylprednisolone—sterile meningitis and arachnoiditis (related to polyethylene preservative)
- Swelling, tenderness, warmth, infection, post-injection pain are-up—can last up to 2 days. Soft tissue atrophy, depigmentation, periarticular calci cations, and tendon rupture

Systemic S/Es:

- Minimal changes in fasting blood glucose or lipid levels after a single epidural injection of dexamethasone usually
- Depot preparations used for epidural injections may produce ACTH suppression and Cushing's syndrome lasting up to a few weeks, even following a single epidural injection of 60 mg of methylprednisolone or triamcinolone
- Single lumbar epidural injection of triamcinolone 80 mg can cause profound HPA axis suppression for 3 weeks and marked reduction in insulin sensitivity
- Intra-articular steroid injections—patients can have detectable levels in circulation

More serious S/Es with long-term supraphysiological doses:

Immunosuppressive:

Chickenpox and measles are of particular concern

Allergy

Endocrine: secondary adrenocortical insu ciency and atrophy (3 months minimum after treatment cessation), hypopituitarism, Cushing's syndrome, withdrawal syndrome (headache, pyrexia, myalgia), often called 'steroid pseudorheumatism'

Increased blood glucose, predisposition to diabetes, worsened pre-existing diabetes, increased appetite and weight gain

Psychiatric: a ective and psychotic disorders, insomnia, confusion

Neurological: amnesia, dizziness, headaches, vertigo

Ocular: cataracts, glaucoma, exophthalmos, retinal detachment

Cardiac: dyslipidaemia, hypertension

Vascular/haematological: increased thrombosis risk, leucocytosis

GI: peptic ulcer, GI perforation, oesophagitis, oesophageal candidiasis, nausea and vomiting, dyspepsia, abdominal distension, peritonitis, pancreatitis

MSK: osteoporosis, growth retardation, muscular weakness and atrophy, osteonecrosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, arthralgia, myalgia, tendon rupture

Renal and urinary: caution in renal insu ciency

Dermatological: impaired wound healing, thin and fragile skin and atrophy, hirsutism, petechiae, erythema, hyperhidrosis, hyper- or hypopigmentation, rash, pruritus, acne, suppression of skin tests

Reproductive: irregular menstruation

Pharmacokinetics

Absorption: small and lipid-soluble, readily absorbed from GI tract, enter target cells by simple di usion

Distribution: transported in plasma by corticosteroid-binding globulin (CBG) and albumin—do not bind to synthetic steroids readily. CBG has low capacity and may become saturated when therapeutic doses of steroids are used. Albumin binds both natural and synthetic steroids. CBG and albumin-bound steroids are biologically inactive

Metabolism: by CYP3A enzyme system, reduction of the double bond between C4 and C5; occurs mainly in hepatocytes. Cortisone and prednisone are inactive until converted *in vivo* to hydrocortisone and prednisolone, respectively. Cortisol (hydrocortisone) is an active agent, whereas the inactive drug cortisone must be converted by the liver to cortisol for biological activity

Excretion: renal

Analgesic e cacy

No di erence in pain and function scores between particulate and non-particulate steroids

Epidural corticosteroids: NNT 7 for 75% pain relief at 60 days, 13 for 50% pain relief at 1 year

Transforaminal: steroid onto ventral aspect of nerve root sleeve and dorsal aspect of disc herniation is theoretically more e ective

E cacy less with radicular pain that has lasted >3 months and previous back surgery

The less soluble an agent (acetate suspensions), the longer it remains in the joint or epidural space and theoretically the more prolonged e ect

Several recommendations:

Interlaminar and caudal epidural steroid injection (ESI): lower risk due to known vascular anatomy

Cervical transforaminal ESI (TFESI): vertebral artery in the foramen at every level—use non-particulate corticosteroid only

Thoracic TFESI: risk of presence of an artery is higher than lumbar spine, but lower than cervical spine—ribs obscuring ability to detect vascular ow on uoroscopy hence recommend non-particulate corticosteroid

Lumbar TFESI: risk of arterial presence is lowest. Dexamethasone preferred as rst line. Higher-risk particulates should be reserved for patients non-responsive to non-particulate formulations

Non-particulate steroids should be used as rst line for TFESI in all cervical injections and lumbar injections above L3

Contraindications and cautions

Hypersensitivity to the drug or excipient

Should not inject into unstable joints, presence of active infection in or near joints

Should not inject into Achilles tendon

Co-treatment with CYP3A inhibitors—increase risk of systemic S/Es

Live virus vaccines contraindicated in patients receiving immunosuppressive doses of corticosteroids

Inactivated viral or bacterial vaccines—expected serum antibody response may not be obtained

Interactions

CYP3A4 inhibitors—increased plasma concentrations of corticosteroid

CYP3A4 inducers—may need to increase dose

Corticosteroids can reduce e ects of anticholinesterases in myasthenia gravis

Enhanced hypokalaemic e ects with diuretics, carbenoxolone, B2 agonists, and theophylline

Caution with cardiac glycosides—hypokalaemia may result in toxicity

Antagonism of competitive neuromuscular blocking drugs

Renal clearance of salicylates is increased by corticosteroids

Special considerations

Pregnancy:

Variable between individual corticosteroids. Prednisone and prednisolone are inactivated by the placenta

Increased incidence of low birthweights and cataracts in infants

Not known to be teratogenic in humans

Animal studies show increased incidence of cleft palate, and brain development a ected

May theoretically lead to neonatal hypoadrenalism, but rarely clinically important

FDA (Food and Drug Administration) Pregnancy Categories for Drugs: prednisolone is schedule D for rst trimester, and schedule C for second and third trimesters (schedule C = human risk cannot be ruled out; schedule D = evidence of risk to human fetus)

Breastfeeding:

Corticosteroids pass into breast milk, and infants may have a degree of adrenal suppression

Paediatrics:

Dose-related growth retardation which may be irreversible

May accelerate epiphyseal closure

Patients should carry a 'Steroid Treatment' card detailing: prescriber, drug, dosage, and treatment duration

E ects may be enhanced in hypothyroidism and cirrhosis, and reduced in hyperthyroidism

Corticosteroids inhibit growth-promoting e ect of human growth hormone

Additional information

Withdrawal syndrome may occur without evidence of adrenal insu ciency

Particulate corticosteroids particle size order: methylprednisolone > triamcinolone > betamethasone

Recommended corticosteroid for epidural injection: betamethasone > triamcinolone

Proposed mechanisms of injury with corticosteroids:

Inadvertent arterial injection arrow pointing rightwards infarction

Animal studies: direct injection into artery—no neurological injury with dexamethasone

Chemical vascular injury

Direct neurotoxic e ects of additives and preservatives—benzyl alcohol, PEG, polysorbate 80, ethylenediaminetetraacetate (EDTA)

Vasospasm due to needle trauma or dye

Further reading

1. British Pain Society/Faculty of Pain Medicine (RCA) Consensus Statement on the use of Corticosteroids for Neuraxial Procedures in the UK. 2018. https://www.britishpainsociety.org/static/uploads/resources/ les/BPS_FPM_Steroid_Statement_FINAL.pdf
2. Knezevic AA, Jovanovic F, Voronov D, et al. Do corticosteroids still have a place in the treatment of chronic pain. Front Pharmacol 2018;9:1229. https://doi.org/10.3389/fphar.2018.01229
3. Peck TE, Hill SA, Williams M (eds). Pharmacology for Anaesthesia and Intensive Care. 2003. London: Greenwich Medical Media
4. Stannard C, Booth S (eds). Churchill's Pocketbooks of Pain. 2nd edition, 2004. London: Elsevier Churchill Livingstone
5. Electronic Medicines Compendium. https://www.medicines.org.uk/emc

12.2 Triamcinolone acetonide

Name (brands)

Kenalog® intra-articular/IM injection

Presentation

40 mg/mL of sterile aqueous suspension, 1 mL glass vial

Excipient with known e ect: 15 mg/mL of benzyl alcohol

Other excipients: polysorbate 80, sodium carboxymethyl cellulose, sodium chloride

Particulate

Pain-related indications

Intra-articular:

RA, OA with in ammatory component, bursitis, epicondylitis, tenosynovitis

IM (where sustained systemic treatment required):

Collagen disorders, dermatological diseases, rheumatic, GI, or respiratory disorders, neoplastic diseases

Safety and e cacy of administration by other routes are yet to be established

Contraindications/caution

IV, intrathecal, and intraocular routes are contraindicated

Incidence of blindness after nasal turbinate and intralesional injections in the face/head

Routes of administration and dosing

Intra-articular:

Small joints 5–10 mg; large joints up to 40 mg; multiple joint involvement up to 80 mg

For sheaths of short tendons, Adcortyl® injection (triamcinolone acetonide 10 mg/mL) is recommended

IM:

Deep into gluteal muscle to avoid SC fat atrophy. Avoid deltoids

Adults and children >12 years: suggested initial dose 40 mg

Mode of action

High-potency GC, with low mineralocorticoid activity

Pharmacokinetics

Absorption:

May be absorbed into systemic circulation from synovial spaces

Deep IM depot injection: almost 100% bioavailability, absorbed slowly. Provides an extended duration of therapeutic e ect and fewer S/Es, compared with oral therapy

Following a single 80 mg dose, adrenal suppression occurs within 24–48 hours, gradually returning to normal within 3 weeks, correlating with the extended duration of therapeutic action

Metabolism:

Hepatic, CYP3A4 substrate, 6- -hydroxylation

Interactions

Reports of clinically signi cant drug interactions in patients receiving triamcinolone acetonide and ritonavir

Special circumstances

Elderly: common S/Es are more serious, particularly osteoporosis, diabetes, hypertension, hypokalaemia, thin skin, and immunode ciency

Children 6–12 years: suggested initial dose of 40 mg, not recommended in those aged <6 years

Must not be given to premature babies or neonates due to benzyl alcohol; can cause toxic and anaphylactoid reactions in infants and children aged up to 3 years

Pregnancy: crosses the placenta

Breastfeeding: no data available

Additional information

Note: does not contain PEG, hence decreased risk of neurotoxicity

Cost

40 mg/mL (ve vials): £7.45

Further reading

1. Benzon H, Rathmell J, Wu CL, et al. Raj's Practical Management of Pain. 4th edition, 2008. Philadelphia, PA: Elsevier
2. Electronic Medicines Compendium. https://www.medicines.org.uk/emc

12.3 Methylprednisolone acetate

Name (brands)

Depo-Medrone® or Depo-Medrol®
Also available: Depo-Medrone® with lidocaine (methylprednisolone 4%, lidocaine hydrochloride 1%)
Solu-Medrone® or Solu-Medrol®

Presentation

White aqueous sterile suspension for injection
Each vial contains 1, 2, or 3 mL of Depo-Medrone® 40 mg/mL
Excipients—PEG, sodium chloride, myristyl- -picolinium chloride, water for injection
Particulate

Pain-related indications

IM administration (for prolonged systemic e ect in rheumatological disorders)
Intra-articular administration
Periarticular, into bursae, into tendon sheaths (not into the substance of tendons)
Intralesional, e.g. keloid scars

Contraindications/caution

Avoid injection into the deltoid—high incidence of SC atrophy
Avoid intralesional administration too super cially—SC atrophy and depigmentation

Routes of administration and dosing

IM;

Single 80 mg injection expected to last average of 2 weeks

Rheumatic disorders and collagen diseases 40–120 mg (1–3 mL) per week
Intra-articular (RA, OA):

4–80 mg; where appropriate, the dose may be repeated at intervals of 7–35 days
Large joint 20–80 mg; medium joint 10–40 mg; small joint 4–10 mg
Spinal joints, unstable joints, and joints devoid of super cial synovial space are not suitable

Into the bursa, periarticular, into the tendon sheath:

4–30 mg; repeat injections may be necessary

Mode of action

High GC e ects, low mineralocorticoid e ects

Side e ects

Systemic absorption of methylprednisolone occurs following intra-articular injection

Adrenal cortical atrophy occurs if received higher than physiological doses (approximately 6 mg of methylprednisolone) for >3 weeks

Rapid IV administration of methylprednisolone is associated with cardiovascular collapse

Overdose:

Reports of acute toxicity and/or death are rare. No speci c antidote; treatment is supportive. Methylprednisolone is dialysable

Pharmacokinetics

Absorption:

When injected, provides slow release of the active steroid to the target site

Distribution:

Widely distributed into tissues, crosses the BBB, secreted in breast milk. Plasma protein binding: approximately 77%

Metabolism:

Hepatic, inactive metabolites (mainly 20 - and 20 -hydroxymethylprednisolone)

Excretion:

No dose adjustments required in renal impairment

Special circumstances

Paediatrics: infants and children are at particular risk from raised ICP

Elderly: no information to suggest a dose change is warranted

Fertility: impairs fertility in animal studies

Pregnancy: methylprednisolone crosses the placenta

Breastfeeding: excreted in small amounts in breast milk. Up to 40 mg daily is safe. May be theoretical risk of hypoadrenalism in doses higher than this, but bene ts of breastfeeding outweigh this risk

Neonates—avoid as contains benzyl alcohol

Additional information

Enhanced e ect in patients with hypothyroidism

Intrathecal methylprednisolone—promising treatment for PHN

Post-mortem studies of PHN patients noted SC in ammation, and PHN patients may have high levels of IL8 in the CSF. This treatment may theoretically decrease pro-in ammatory mediators (which may contribute to central sensitization), neuraxial in ammation, and PHN pain as a result. Studies have shown a signi cant decrease in PHN pain (both burning and lancinating). CSF concentrations of IL8 were also signi cantly decreased

Cost

1 vial 40 mg/mL = £3.44

1 vial 80 mg/2 mL = £6.18

1 vial 120 mg/3 mL = £8.96

Methylprednisolone acetate 40 mg and lidocaine hydrochloride 10 mg in 1 mL vial = £3.94, 2 mL vial = £7.06

Further reading

1. Vadivelu N, Urman RD, Roberta H. Essentials of Pain Management. 2015. London: Springer
2. Electronic Medicines Compendium. https://www.medicines.org.uk/emc

12.4 Dexamethasone

Presentation

Clear glass ampoule, 1 mL or 2 mL, clear colourless solution

Dexamethasone (Hospira®), 3.3 mg/mL:

- 1 mL solution for injection contains 4 mg of dexamethasone phosphate equivalent to 3.32 mg of dexamethasone base
- Excipients—sodium citrate, disodium edetate, sodium sulphite anhydrous, sodium hydroxide, and hydrochloric acid

Dexamethasone preservative-free (Aspen®) 3.8 mg/mL:

- 1 mL solution for injection contains 5 mg of dexamethasone sodium phosphate equivalent to 3.8 mg of dexamethasone base
- Excipients—glycerol, disodium edetate, sodium hydroxide, or phosphoric acid, stored in the fridge

Non-particulate and devoid of benzyl alcohol and PEG

Pain-related indications

Adjuvant analgesic and symptomatic treatment of cord compression in palliative care settings

Cancer pain: reduces tumour oedema, and thereby pressure on surrounding structures.

Analgesic e ect is greatest in a con ned space:

- Headache associated with raised ICP from cerebral tumours
- Nerve compression pain, often in conjunction with other analgesics/adjuvants
- Malignant bone pain

Particularly useful for neuropathic, visceral, and bone pain syndromes in patients with advanced malignant disease

- Standard dose is 16–24 mg/day, can be given once daily due to its long t1/2, but divided doses usually used to mitigate high-dose toxic e ects such as psychosis and severe blood glucose abnormalities in diabetic patients
- Doses as high as 100 mg may be given in severe pain crises, similar to doses used in acute neurological emergencies
- IV boluses should be given over several minutes to avoid untoward reactions such as burning sensations

Routes of administration and dosing

All dosing recommendations are given in units of dexamethasone base

Dose range usually 4–16 mg/24 hours

Suitable for intra-articular or soft tissue injection

Recurrent or inoperable brain tumours: usually 1.7 mg twice to three times daily

Large joint 1.7–3.3 mg; small joints 0.66–0.8 mg; bursae 1.7–2.5 mg; tendon sheaths 0.33–0.8 mg; soft tissue in ltration 1.7–5 mg

Frequency = ranges from 3 days to 3 weeks

Mode of action

Predominant GC activity and minimal mineralocorticoid activity, making it the least toxic choice

Second highest GC potency after betamethasone

Side e ects

Enhanced GC activity of dexamethasone leads to more hyperglycaemia, compared with other steroids

Sleep disturbance and restlessness may start within hours of a large dose

Pharmacokinetics

Absorption

Well absorbed by mouth and inhalation; following injection, dexamethasone is rapidly hydrolysed to dexamethasone, with peak plasma levels within 5 minutes

Distribution:

Plasma protein binding approximately 77% (less than most other corticosteroids)

Penetrates into tissue uid and CSF

Metabolism:

High uptake by the liver, kidneys, and adrenal glands, with slow hepatic metabolism

Plasma t1/2 3.5–4.5 hours, but e ects outlive plasma concentrations; thus, biological t1/2 is of greater relevance (36–54 hours)

Excretion:

Up to 65% of a dose excreted in the urine in 24 hours, mainly as unconjugated steroids

Special circumstances

Neonates: only preservative-free solutions should be administered

Paediatrics: dosage should be limited to a single dose on alternate days

Pregnancy: readily crosses the placenta, with minimal inactivation

Breastfeeding: no data available for dexamethasone

Palliative care: can be diluted with sodium chloride and given by continuous subcutaneous infusion (CSCI)

Additional information

Burning or tingling after IV administration, particularly in perineal area

Number and activity of spermatozoa may be a ected in men

Theoretical disadvantages: easy washout from epidural space, reports of convulsions after intrathecal injection in animals

Has been shown to prolong anaesthesia and analgesia, alongside LA, in nerve blockade

Cost

500 mcg (28 tablets): £6.40
2 mg (50 tablets): £6.84
4 mg (50 tablets): £83
Dexamethasone (base) 3.3 mg/mL (ten ampoules) = £15.00–22.63
Dexamethasone (base) 6.6 mg/2 mL (ten ampoules) = £22.00–24.00

Further reading

1. Electronic Medicines Compendium. https://www.medicines.org.uk/emc
2. Drugs.com. Dexamethasone. https://www.drugs.com/ingredient/dexamethasone.html

12.5 Hydrocortisone

Presentation

Hydrocortisone acetate 25 mg/mL suspension for injection
IV/IM—white powder as sodium succinate, for reconstitution with water for injection
Glass ampoule, suspension for injection
Excipients: benzyl alcohol, sodium chloride, sodium carboxymethyl cellulose, polysorbate 80)

Pain-related indications

Intra-articular or periarticular: for RA and OA, when few joints are involved
Non-articular: for symptomatic treatment of in ammatory conditions such as in amed tendon sheaths and bursae

Contraindications/caution

Injection into spinal or other non-diarthrodial joints

Routes of administration and dosing

Intra-articular: 5–50 mg, depending on size of patient and joint
May be repeated at intervals of 21 days
No more than three joints should be treated on any one day
Adults: 5–50 mg, depending on joint size
Children: 5–30 mg daily in divided doses

Mode of action

Both GC and mineralocorticoid activity
Cortisone has minimal activity and must be converted to hydrocortisone in the liver rst

Side e ects

Overdose: no speci c antidote available. Symptoms: nausea and vomiting, sodium and water retention, hyperglycaemia, GI bleeding
Treatment is symptomatic

Pharmacokinetics

Absorption:

Slow systemic absorption following intra-articular or soft tissue injection. Onset after IV/IM injection is 2–4 hours; lasts 8 hours

Distribution:

Plasma protein binding >90%

Metabolism:

Metabolized in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol

Excretion:

In the urine, mainly as conjugated glucuronides, and a very small proportion is excreted unchanged

Special circumstances

Pregnancy: cortisone readily crosses the placenta

Breastfeeding: no speci c data available for cortisone. Doses of up to 200 mg daily unlikely to cause systemic e ects in infants

Additional information

Hydrocortisone is dialysable

In overdose, can administer IV cimetidine or ranitidine to prevent GI bleeding

Cost

10 mg and 20 mg (30 tablets): £7.04–7.52

100 mg/mL solution for injection (ve ampoules): £10.60

Hydrocortisone cream 0.5% and 1% (15 g): £1.07–1.22 (2.5% = £4.99)

Further reading

1. Smith T, Pinnock C, Lin T. Fundamentals of Anaesthesia. 4th edition, 2016. Cambridge: Cambridge University Press
2. Electronic Medicines Compendium. https://www.medicines.org.uk/emc

12.6 Betamethasone

Name (brands)

Celestone® or Betnesol® 4 mg/mL solution for injection (betamethasone acetate) = soluble ester with rapid action, particulate

Soluspan® (betamethasone)—only slightly soluble, a ords sustained activity, considered non-particulate, given its soluble nature, not commercially available

Celestone® Soluspan®—commercially available; contains both betamethasone acetate and phosphate and shows extensive aggregation of particles; reported cases of paralysis in the literature

Presentation of Betnesol®

1 mL ampoule contains a clear colourless or pale yellow, sterile aqueous solution

Each ampoule contains 5.3 mg of betamethasone sodium phosphate is equivalent to 4 mg of betamethasone

Excipients with known e ect: sodium metabisulphite 0.1% w/v, 0.678 mg sodium per mL

Pain-related indications

Soft tissue lesions, e.g. tennis elbow, tenosynovitis, bursitis

Contraindications/caution

Not recommended intrathecally

Routes of administration and dosing

Can be given slow IV, deep IM, subconjunctivally, or as local soft tissue injection, depending on indication

Local injection dose = 4–20 mg in adults, smaller doses in children. This dose can be repeated on 2–3 occasions, depending on response (up to four times in 24 hours)

Mode of action

Has the highest GC potency, and although it is a depot-type injectate, it has the least particulate material

Pharmacokinetics

Following IM injection—betamethasone appears to be readily absorbed, with peak plasma concentration detected at 12.92 hours

Interactions

Concomitant use of betamethasone with quetiapine may result in increased metabolism of quetiapine, so a higher dose may be needed

Special circumstances

Pregnancy: betamethasone readily crosses the placenta. May result in transient suppression of fetal heart rate (FHR)

Myocardial hypertrophy and gastro-oesophageal re ux have been reported in association with *in utero* exposure to betamethasone

Additional information

Betamethasone acetate thought to act as prodrug or reservoir, conferring extended-release characteristics

Cost

4 mg/1 mL solution for injection (ve ampoules): £30.26

0.1% cream (30 g): £1.14

Further reading

1. Electronic Medicines Compendium. https://www.medicines.org.uk/emc
2. Salem II, Najib NM. Pharmacokinetics of betamethasone after single-dose intramuscular administration of betamethasone phosphate and betamethasone acetate to healthy

subjects. Clin Ther 2012;34(1):214–20. https://www.clinicaltherapeutics.com/article/S0149-2918(11)00774-0/pdf

12.7 Steroid passport

For an example of a steroid passport used at the University Hospitals of Leicester, see Figs. 12.7.1 and 12.7.2

Patients/doctors can document the steroid-based interventions which patients receive from various specialties

Steroid injections

Steroids that are injected into muscles or joints may cause some pain and swelling at the site of the injection, but this should pass within a few days

Steroid injections can also cause muscle or tendon weakness on repeated injections

Because of the risk of side e ects, steroid injections are often only given at intervals of at least 4 months and a maximum of three injections in a year is usually recommended

Please kindly keep this passport safe and ask your doctor to fill in this passport every time you have a steroid injection. It is very important to carry this passport every time you have an injection.

No	Date of injection	Type of steroid	Dosage in mgs
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Post procedure care following chronic pain intervention

- Use ice (cold) packs on the treated area today
- Use warmth on the treated area from tomorrow
- Take your regular pain medications as usual
- Don't worry if your pain gets worse for the first few days immediately after your injection. This is known as flare up pain
- If the injection has helped you may be offered a repeat injection if appropriate. If you get no benefit from the injection you may go to your GP to be referred back to the pain clinic for further assessment and discuss further management options
- Injection treatment is one of the multiple options for pain management and they are not cure for your pain
- Use any time you have reduced pain to work on any physiotherapy exercises you may have been doing

Figure 12.7.1 Example of a steroid passport used at the University Hospitals of Leicester

Copyright © University Hospitals of Leicester

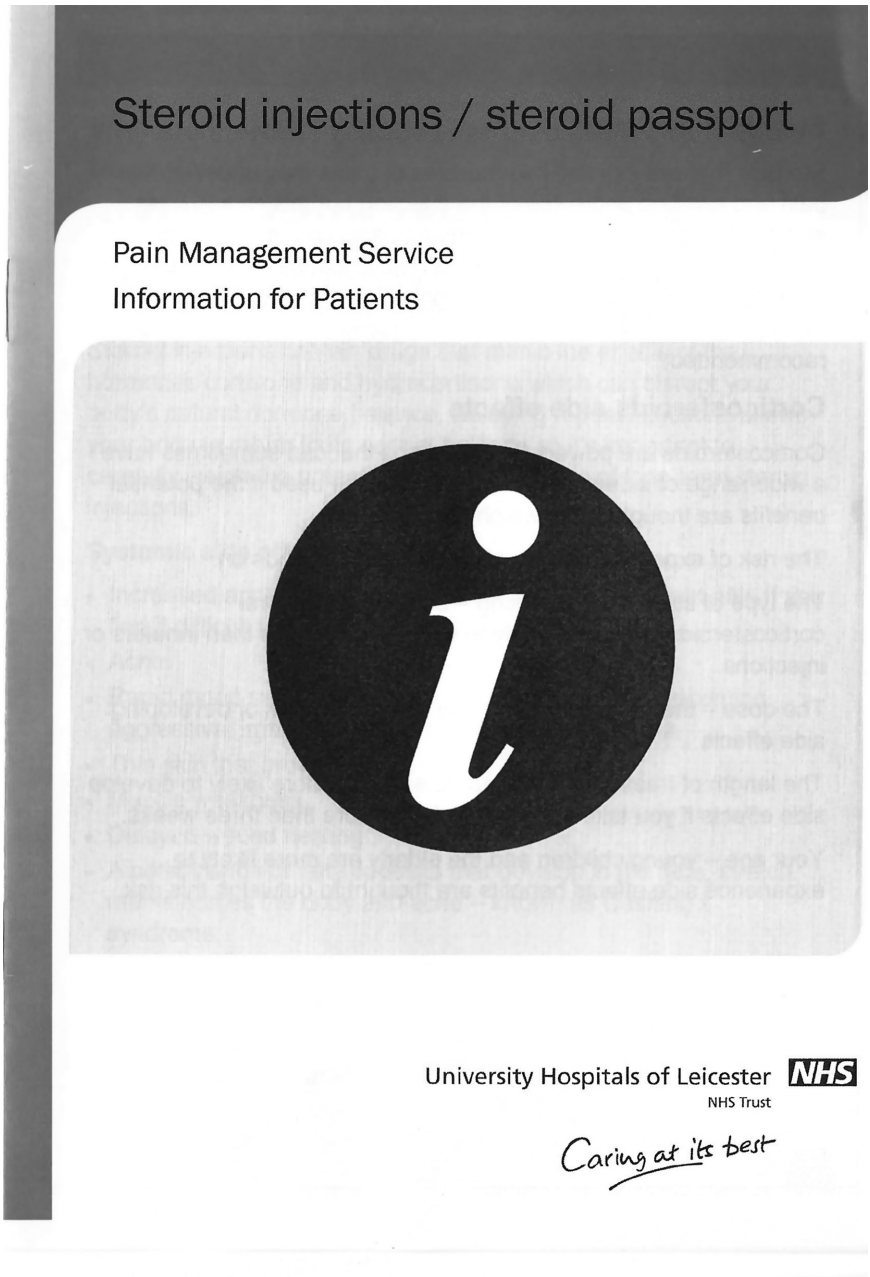
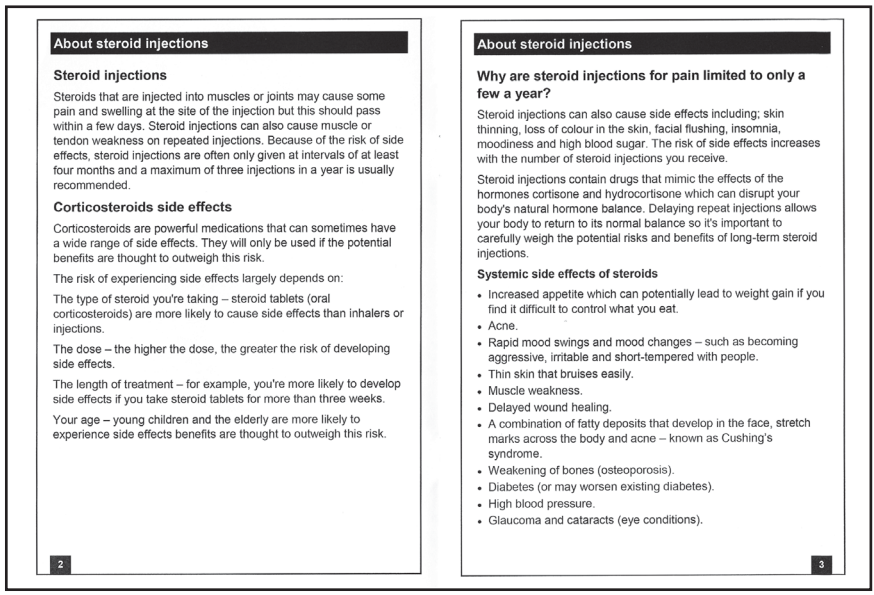


Figure 12.7.2 Steroid passport as a booklet
Copyright © University Hospitals of Leicester



About steroid injections

Steroid injections

Steroids that are injected into muscles or joints may cause some pain and swelling at the site of the injection but this should pass within a few days. Steroid injections can also cause muscle or tendon weakness on repeated injections. Because of the risk of side effects, steroid injections are often only given at intervals of at least four months and a maximum of three injections in a year is usually recommended.

Corticosteroids side effects

Corticosteroids are powerful medications that can sometimes have a wide range of side effects. They will only be used if the potential benefits are thought to outweigh this risk.

The risk of experiencing side effects largely depends on:

The type of steroid you're taking – steroid tablets (oral corticosteroids) are more likely to cause side effects than inhalers or injections.

The dose – the higher the dose, the greater the risk of developing side effects.

The length of treatment – for example, you're more likely to develop side effects if you take steroid tablets for more than three weeks.

Your age – young children and the elderly are more likely to experience side effects benefits are thought to outweigh this risk.

2

About steroid injections

Why are steroid injections for pain limited to only a few a year?

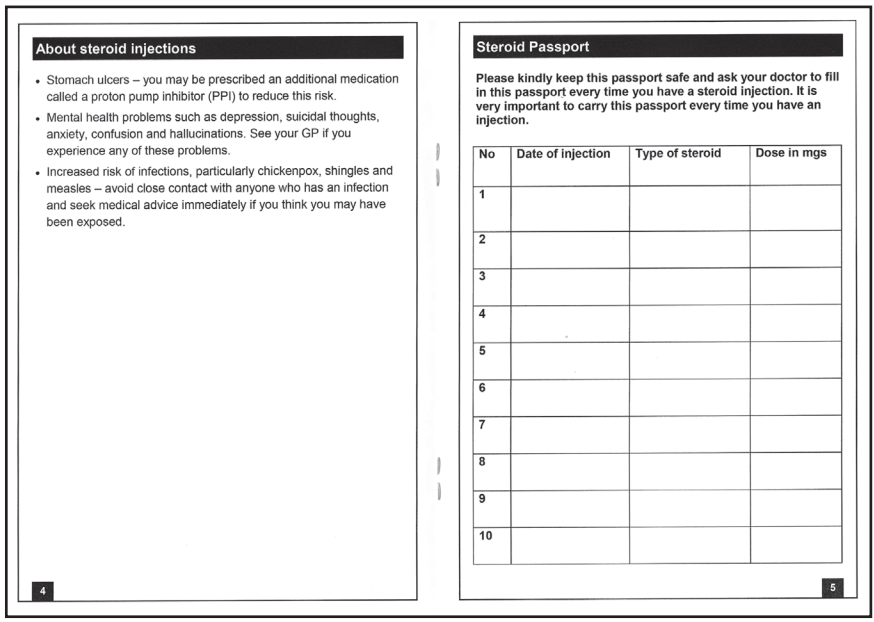
Steroid injections can also cause side effects including; skin thinning, loss of colour in the skin, facial flushing, insomnia, moodiness and high blood sugar. The risk of side effects increases with the number of steroid injections you receive.

Steroid injections contain drugs that mimic the effects of the hormones cortisone and hydrocortisone which can disrupt your body's natural hormone balance. Delaying repeat injections allows your body to return to its normal balance so it's important to carefully weigh the potential risks and benefits of long-term steroid injections.

Systemic side effects of steroids

- Increased appetite which can potentially lead to weight gain if you find it difficult to control what you eat.
- Acne.
- Rapid mood swings and mood changes – such as becoming aggressive, irritable and short-tempered with people.
- Thin skin that bruises easily.
- Muscle weakness.
- Delayed wound healing.
- A combination of fatty deposits that develop in the face, stretch marks across the body and acne – known as Cushing's syndrome.
- Weakening of bones (osteoporosis).
- Diabetes (or may worsen existing diabetes).
- High blood pressure.
- Glaucoma and cataracts (eye conditions).

3



About steroid injections

- Stomach ulcers – you may be prescribed an additional medication called a proton pump inhibitor (PPI) to reduce this risk.
- Mental health problems such as depression, suicidal thoughts, anxiety, confusion and hallucinations. See your GP if you experience any of these problems.
- Increased risk of infections, particularly chickenpox, shingles and measles – avoid close contact with anyone who has an infection and seek medical advice immediately if you think you may have been exposed.

4

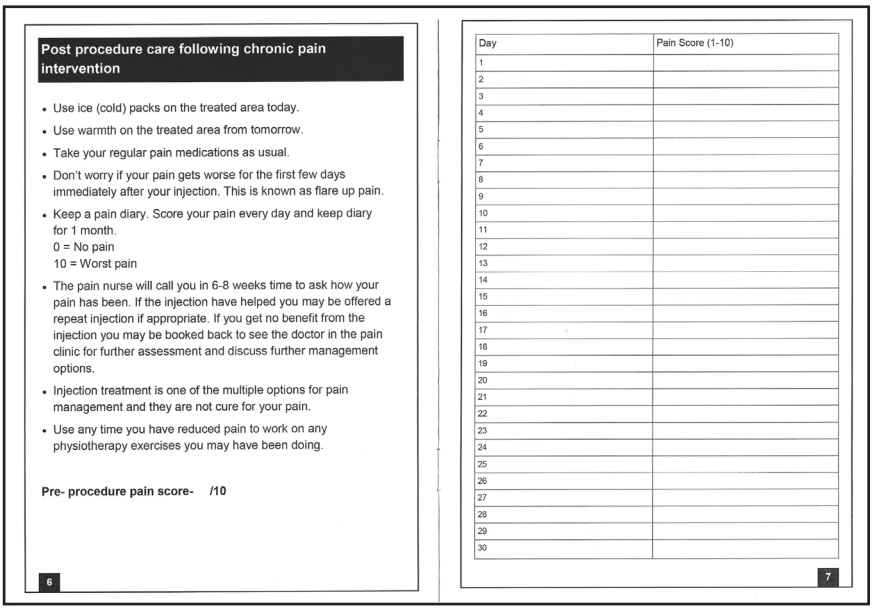
Steroid Passport

Please kindly keep this passport safe and ask your doctor to fill in this passport every time you have a steroid injection. It is very important to carry this passport every time you have an injection.

No	Date of injection	Type of steroid	Dose in mgs
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

5

Figure 12.7.2 Continued



Post procedure care following chronic pain intervention

- Use ice (cold) packs on the treated area today.
- Use warmth on the treated area from tomorrow.
- Take your regular pain medications as usual.
- Don't worry if your pain gets worse for the first few days immediately after your injection. This is known as flare up pain.
- Keep a pain diary. Score your pain every day and keep diary for 1 month.
  0 = No pain
  10 = Worst pain
- The pain nurse will call you in 6-8 weeks time to ask how your pain has been. If the injection have helped you may be offered a repeat injection if appropriate. If you get no benefit from the injection you may be booked back to see the doctor in the pain clinic for further assessment and discuss further management options.
- Injection treatment is one of the multiple options for pain management and they are not cure for your pain.
- Use any time you have reduced pain to work on any physiotherapy exercises you may have been doing.

Pre- procedure pain score- /10

6

Day	Pain Score (1-10)
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
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13	
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25	
26	
27	
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29	
30	

7

Figure 12.7.2 Continued

Corticosteroid side e ects

Corticosteroids are powerful medications that can sometimes have a wide range of side e ects

They will only be used if the potential bene ts are thought to outweigh this risk

The risk of experiencing side e ects largely depends on

The type of steroid you are taking—steroid tablets (oral corticosteroids) are more likely to cause side e ects than inhalers or injections

The dose—the higher the dose, the greater the risk of developing side e ects

The length of treatment—for example, you are more likely to develop side e ects if you take steroid tablets for more than three weeks

Your age—young children and the elderly are more likely to experience side e ects; bene ts are thought to outweigh this risk

Why are steroid injections for pain limited to only a few a year?

Steroid injections can also cause side e ects, including skin thinning, loss of colour, facial ushing, insomnia, moodiness, and high blood sugar

The risk of side e ects increases with the number of steroid injections you receive

Steroid injections contain drugs that mimic the e ect of the hormones cortisone and hydrocortisone, which can disturb your body's natural hormone balance

Delaying repeat injections allows your body to return to its normal balance, so it is important to carefully weigh the potential risks and bene ts of long-term steroid injections

Systemic side e ects of steroids

Increased appetite which can potentially lead to weight gain if you nd it di cult to control what you eat

Acne

Rapid mood swings and mood changes—such as becoming aggressive, irritable, and short-tempered with people

Thin skin that bruises easily

Muscle weakness

Delayed wound healing

A combination of fatty deposits that develop in the face, stretch marks across the body, and acne—known as Cushing's syndrome

Weakening of bones (osteoporosis)

Diabetes (or may worsen existing diabetes)

High blood pressure

Glaucoma and cataracts (eye conditions)

Stomach ulcers—you may be prescribed an additional medication called a proton pump inhibitor (PPI) to reduce this risk

Mental health problems such as depression, suicidal thoughts, anxiety, confusion, and hallucinations. See your GP if you experience any of these problems

Increased risk of infections, particularly chickenpox, shingles, and measles—avoid close contact with anyone who has an infection, and seek medical advice immediately if you think you may have been exposed

Post-procedure care following chronic pain intervention

Use ice (cold) packs on the treated area today

Use warmth on the treated area from tomorrow

Take your regular pain medications as usual

Don't worry if your pain gets worse for the rst few days immediately after your injection. This is known as are-up pain

If the injection has helped, you may be o ered a repeat injection if appropriate. If you get no bene t from the injection, you may go to your GP to be referred back to the pain clinic for further assessment and discuss further management options

Injection treatment is one of the multiple options for pain management and they are not a cure for your pain

Use any time you have reduced pain to work on any physiotherapy exercises you may have been doing

CHAPTER 13

Miscellaneous

Hadi Bedran, Udaya Chakka, Bethany Fitzmaurice, Praveen Ganty, James Jack, Peter Keogh, Arumugam Pitchiah, Kavita Poply, Manamohan Rangaiah, Jan Rudiger, Maria Stasiowska, Ali a Tameem, and Matthew Wong

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13.1 Baclofen

Indications

Painful spasticity from MS, spinal lesions, cerebral events, or other pathologies causing pain from muscle spasms

Limited role as monotherapy for primary treatment of pain

Contraindications

Precaution in diabetics, stroke, peptic ulceration, renal/respiratory/hepatic failure

Avoid in patients with mental health disorders, seizures, and heart failure (negative inotropic e ect)

Intrathecal delivery in patients with contraindications to invasive neuromodulation

Dose

Oral administration:

- Usually high doses are required for analgesia
- Normally started at 5 mg 2–3 times daily
- Usual daily dose: 5–10 mg three times daily
- Maximum daily dose: 120 mg
- Children: 0.3 mg/kg/day
- Reduced doses in renal impairment

Intrathecal administration (see 20.8 Intrathecal drug delivery systems, p. 384):

- Only used in selective cases of severe neuropathic/nociceptive chronic painful spasticity refractory to oral antispastic drugs and conservative treatments

Trial of intrathecal baclofen should be done before implanting an external or internal intrathecal pump system. Some institutions perform 2-3 diagnostic blocks 24 hours apart of a single shot baclofen intrathecal administration 25mcg, 50mcg and 75-100mcg in a monitored health care setting. Test dose is performed to assess e ectiveness, adverse e ects and determine the starting dose of baclofen if a pump is inserted

Tolerance/tachyphylaxis occurs in a fth of patients

Doses of above 1 mg daily are normally not recommended

Mode of action

Depression of monosynaptic and polysynaptic re ex transmission by stimulating $GABA_B$ receptors. Secondary e ect may be inhibition of glutamate and aspartate

Monitoring

Careful adjustment is often necessary to meet the requirements of each individual patient

Elevated aspartate aminotransferase, alkaline phosphatase, and glucose have been recorded. These should be monitored in patients with liver disease or diabetes mellitus

Side e ects

Very common: sedation, somnolence, nausea

Common: dry mouth, respiratory depression, light-headedness, confusion, dizziness, headache, insomnia, depression, euphoric mood, myalgia, ataxia, tremor, nystagmus, hallucination, nightmare, visual impairment, GI disorder, rash

Rare: abdominal pain, abnormal LFTs, dysarthria, erectile dysfunction, paraesthesiae, taste disturbances, urinary retention

Relevant pharmacokinetics

Absorption: rapidly and completely absorbed after oral administration. Peak plasma concentrations 0.5–1.5 hours after oral administration

Distribution: active substance concentrations are approximately 8.5 times lower in the CSF than in the plasma

Metabolism: minimal. Deamination yields a pharmacologically inactive metabolite

Excretion: plasma elimination t1/2 is 3–4 hours. Excreted largely unchanged in the urine

Renal impairment: dosage adjustment is required

Hepatic impairment: no change in dose required

Relevant pharmacodynamics

CNS depressant properties and anti-nociceptive e ects

Increased gastric acid secretion

Interactions

Antidepressants: pronounced muscular hypotonia

Antihypertensives: marked hypotension

CNS depressants: increased sedation and risk of respiratory depression

Lithium: aggravated hyperkinetic symptoms

Levodopa/dopa decarboxylase inhibitors: confusion, hallucinations, agitation, worsening symptoms of parkinsonism

Opioids: enhanced CNS and respiratory depressant e ects of opioids

Special circumstances

Pregnancy: crosses the placental barrier and should be avoided

Breastfeeding: quantities of active substance passing into breast milk are unlikely to cause undesirable e ects in infants

Children: can be used for pain from muscular spasticity of cerebral origin or secondary to spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin

Driving: patients experiencing adverse reactions such as dizziness, somnolence, and visual impairment should be advised to refrain from driving or operating machinery

Additional information

Patient selection: it is likely to be of most bene t in patients whose spasticity constitutes a severe handicap to their activities

Abrupt withdrawal can cause:

- Confusion, delirium, hallucination, psychosis, dyskinesia, tachycardia, hyperthermia
- Serotonin syndrome
- Temporary aggravation of spasticity
- Can be life-threatening in patients on high doses (mainly patients on intrathecal baclofen pumps)

Overdose can present with somnolence, respiratory depression, seizures, hypotonia, autonomic instability, and bradycardia

Excipients: baclofen tablets contain lactose

Alternative medications with antispasmodic properties that can be considered include botulinum toxin, dantrolene, NSAIDs, BZDs, topiramate, gabapentin/pregabalin, and tizanidine

Cost

10 mg (84 tablets): £1.64

Oral solution 5 mg/5 mL for 300 mL bottle: £4.72

Further reading

1. British National Formulary. Baclofen. https://bnf.nice.org.uk/drug/baclofen.html
2. NHS Commissioning Board Clinical Reference Group for Neurosciences. Clinical commissioning policy: intrathecal baclofen (ITB). 2013. https://www.england.nhs.uk/wp-content/uploads/2013/04/d04-p-c.pdf
3. Electronic Medicines Compendium. Baclofen tablets 10mg. https://www.medicines.org.uk/emc/product/2594/smpc

13.2 Bisphosphonates

Introduction, class of drugs

Bisphosphonates are commonly prescribed for the prevention and treatment of a range of skeletal conditions where there exists an imbalance between bone formation and bone resorption

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate, a naturally occurring compound in which two phosphate groups are linked by esteri cation

Generally, they are available in generic names.

Table 13.2.1 Classi cation of bisphosphonates

Bisphosphonates	Examples	Relative potencies for osteoclast inhibition
First generation	Etidronate	1
	Tiludronic acid	10
Second generation	Pamidronate	100
	Alendronic acid	500
	Ibandronic acid	1000
Third generation	Risedronate	2000
	Zoledronic acid	10 000

Pamidronate is an amino-bisphosphonate, available in 3 mg/mL, 9 mg/mL, and 15 mg/mL concentrations.

(See Table 13.2.1.)

They can also be divided into non-nitrogen-containing (earlier generation) and nitrogen-containing (newer generation which are more potent).

Indications

Primary agents in the management of conditions associated with osteoclast-mediated bone loss due to osteoporosis, Paget's disease of bone, bony metastasis, multiple myeloma, and hypercalcaemia of pregnancy

Also used in the treatment of heritable skeletal disorders in children and postmenopausal and GC- and transplant-induced osteoporosis

In chronic pain, pamidronate is used for the management of early CRPS

Contraindications

Previous hypersensitive reactions to other bisphosphonates and mannitol

Cautioned in patients with elderly with cardiac disease, previous thyroid surgery, patients at risk of hypocalcaemia—may precipitate symptomatic hypocalcemia including tetany and renal impairment

Routes of administration and dosing

Bisphosphonates can be administered by either oral or parenteral route

Parenteral route can be considered for use in patients with contraindications to oral bisphosphonates (e.g. oesophageal disease, inability to sit up right after an oral dose, expected poor adherence to oral route, failure to respond with oral agents). However, recent development of pharmacologically equivalent oral preparations, allowing either once-weekly or once-monthly administration, has improved patient compliance

Osteoporosis

1. Alendronic acid 10 mg daily or 70 mg once weekly
2. Risedronate 5 mg once daily; alternately 35 mg once weekly

Early CRPS

Patients with suspected/established CRPS (especially in the first 6 months of presentation) may benefit from a single dose of pamidronate 60 mg by IV administration

Mechanism of action

The main mechanism is inhibition of bone resorption

Bisphosphonates have a very high affinity for mineralized bone, like their natural analogue pyrophosphate. Bisphosphonates strongly adsorb to hydroxyapatite (calcium phosphate) crystals in bone, which may reduce bony dissolution

They also inhibit osteoclast activity

Bisphosphonates also function to limit both osteoblast and osteoclast apoptosis

Monitoring

Assessment of renal function plays an important role. Regular checking of serum electrolytes, Ca^{2+}, and phosphates are needed, as electrolyte imbalance can cause convulsions in vulnerable patients

Dental examination is advisable prior to initiation of treatment in vulnerable patients

Adverse effects

Hypertension, injection site reaction, alopecia, loss of appetite, anaemia, arthralgia, constipation, diarrhoea, influenza-like illness, malaise, anaphylactic reaction, and bronchospasm

Specific risks

Arthralgia

Osteonecrosis of the jaw: can occur predominantly in cancer patients receiving chemotherapy or corticosteroids and with certain pre-existing dental conditions (periodontal disease, poorly fitting dentures, or local trauma). Dental examination is recommended prior to treatment

Atypical femur fracture: often bilateral fractures with minimal or no trauma were reported. This risk increases in patients taking GCs

Potential increased risk of atrial fibrillation (more studies are warranted)

Pharmacodynamics and kinetics

Bisphosphonates are poorly absorbed through the GI tract

The oral bioavailability of alendronate, risedronate, and ibandronate ranges from 0.6% to 1%

The oral dosing of bisphosphonates requires consumption on an empty stomach, with advice for no food intake for nearly 60 minutes

The skeleton takes up 50% of the absorbed drug, with the remainder excreted unchanged by the renal route

Pamidronate is not metabolized in the human body; its elimination t1/2 is 28 hours ± 7 hours, and the renal route is the main route of excretion. Avoid if the GFR is <30 mL/min/1.73 m^2. No dose adjustment is necessary in mild to moderate hepatic impairment

Special circumstances

Avoid in pregnancy (may cause fetal effects) and in breastfeeding

Cost

Pamidronate disodium 60 mg/20 mL solution: £110

Further reading

1. Cremers S, Drake MT, Ebetino FH, et al. Pharmacology of bisphosphonates. Br J Clin Pharmacol 2019;85:1052–62
2. Giusti A, Bianchi G. Treatment of complex regional pain syndrome type 1 with bisphosphonates. RMD Open 2015;1:e000056.
3. Joint Formulary Committee. British National Formulary. London: 2020. BMJ Group and Pharmaceutical Press. https://www.bnf.org

13.3 Botulinum toxin

Class of drug and brand names

Botulinum toxin type A (BTX-A): Azzalure® (Galderma), Bocouture® (Merz), Botox® (Allergan), Dysport® (Ipsen), Xeomin® (Merz)

Botulinum toxin type B (BTX-B): Neurobloc® (Eisai)

Indications

Licensed for use in overactive bladder, urinary incontinence from detrusor overactivity, prophylaxis of chronic migraine, spasticity in cervical dystonia, axillary hyperhidrosis, blepharospasm associated with dystonia, and strabismus (children)

Unlicensed for use in prophylaxis of episodic migraine, upper or lower limb spasticity in children, trigeminal neuralgia, neuropathic pain, and myofascial pain

Contraindications

Hypersensitivity to botulinum toxin or components in the formulation

Infection

Urinary tract infection or retention when used for intradetrusor injections

Caution

Risk of respiratory failure and/or swallowing difficulties from muscular paralysis in patients

Bronchitis and upper respiratory tract infections with Botox® injections for upper limb spasticity

Compromised respiratory/bulbar function with parotid/neck muscle injections

Neuromuscular disorders

Dose

Maximal cumulative dose should not exceed 400 units in a 3-month interval

Individual doses injected vary per muscle group and indication for injection

Mode of action

Blocks the release of ACh from cholinergic neurons at the NMJ, autonomic ganglia, post-ganglionic parasympathetic nerve terminals, and sympathetic nerve endings that release ACh

Inhibits the release of GABA, noradrenaline, and glutamate in the brain and spinal cord

Central and peripheral actions on sensory nerves:

- Inhibits CGRP and SP production at the DRG
- Inhibits the release of pro-inflammatory and nociceptive NTs in the peripheral nervous system and dorsal horn

Attenuates neuroin ammation and central sensitization

Relevant pharmacokinetics/pharmacodynamics

Local e ects from IM Botulinum injections—produce transient accid paralysis

Onset of action is 24–72 hours

Peak e ect at 5–7 days

Duration of action for 8–12 weeks

Side e ects

Common adverse reactions (5%) from injections in the following conditions:

Overactive bladder/detrusor instability: urinary tract infection, dysuria, urinary retention

Chronic migraine: neck pain, headache

Spasticity: pain in extremity

Cervical dystonia: dysphagia, upper respiratory tract infection, neck pain, headache, increased cough, u syndrome, back pain, rhinitis

Axillary hyperhidrosis: injection site pain and haemorrhage, non-axillary sweating, pharyngitis, u syndrome

Interactions

Potentiated e ect of Botulinum when used with aminoglycosides, neuromuscular blockers/muscle relaxants, Mg^{2+}

Special circumstances

Pregnancy: may cause fetal harm

Breastfeeding: avoid; low risk of systemic absorption

Children: safety and e cacy only established in patients <16 years old for treating cervical dystonia, and in those <12 years old for treating blepharospasm and strabismus

Cost

Xeomin® and Bocouture®, 50-unit vial: £72

Allergan® 300-unit vial: £276

Further reading

1. Joint Formulary Committee. Botulinum toxin type A. British National Formulary (online). London: BMJ Group and Pharmaceutical Press
2. Oh HM, Chung ME. Botulinum toxin for neuropathic pain: a review of the literature. Toxins (Basel) 2015;7(8):3127–54

13.4 Calcitonin

Introduction

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland, with a primary role in Ca^{2+} homeostasis

Evidence of calcitonin for pain management is controversial and mostly from small studies

Indications

Disorders of bone metabolism: osteoporosis, Paget's disease, hypercalcaemia of malignancy, and prevention of acute bone loss due to sudden immobilization (e.g. after a fracture)

Phantom limb pain: e ective in acute phantom limb pain (<7 days post-amputation), but not in the chronic setting

Acute pain from osteoporotic vertebral fractures and bony metastases

Refractory neuropathic pain

Contraindications

Hypocalcaemia

Caution in heart failure as can reduce cardiac output

Dosage

Preparations: salmon calcitonin (IV, IM, SC, and intranasal preparations) and intranasal preparations of calcitonin

Hypercalcaemia and prevention of acute bone loss due to sudden immobilization: 100 units in single or divided doses (less than daily dose of 400 units) SC or IV

Phantom limb pain: 200 units SC or IV in 100 mL of normal saline for 3 days

Children 5–10 units/kg IV in normal saline administered over 6 hours

Treatment limited to the shortest possible time to minimize the risk of malignancy. Poor-quality evidence suggests an association between calcitonin and cancer development

Mode of action

Mechanism of action in pain relief is unclear. Some hypotheses include:

- Inhibition of osteoclastic bone resorption, altering both the number and/or the resorptive activity of osteoclasts
- Binding to calcitonin receptors on serotonergic neurons in the thalamus, PAG matter, and raphe nucleus, targeting the descending inhibitory pain pathways
- Normalization of Na^+ channel expression on damaged peripheral nerves
- Reduced production of cytokines and in ammatory PGs peripherally
- Potential binding to opioid receptors (kappa or delta) and release of endogenous -endorphins

Pharmacokinetics

Bioavailability: 65–70%, normally given IV, SC, or IM

Terminal t1/2: approximately 60 minutes following IM or SC administration

Apparent Vd: 0.15–0.3 L/kg

Metabolism: mostly to inactive metabolites in the kidney, blood, and peripheral tissues

Interactions

Reduces the concentration of lithium

Special circumstances

Believed to be safe in pregnancy: does not cross the placental barrier. However, assess on an individual case basis and consider risk versus bene t for both mother and fetus. Contact your local department of medicines information for advice

Not established if safe during lactation and in children. Human data lacking, but excretion into milk not expected as calcitonin has a high molecular weight. Calcitonin has been shown to inhibit lactation in animals

Adverse e ects

Can lead to hypocalcaemic tetany if the patient was hypocalcaemic before administration

Common: nausea, vomiting, facial ushing, diarrhoea, thrombophlebitis, headaches, drowsiness. Antiemetics are commonly given pre-emptively to prevent nausea and vomiting

Cancer: the Committee for Medicinal Products for Human Use found that a higher proportion of patients treated with calcitonin for long periods of time develop cancer of various types, compared with patients taking placebo. The increase in cancer rates ranged from 0.7% (oral formulation) to 2.4% (nasal formulation). The studies have poor-quality cancer assessment methodology and calcitonin continues to have a licence for its clinical use

Cost

Injectable solution: ve ampoules (50 units/mL): £167

Injectable solution: ve ampoules (100 units/mL): £220

Injectable solution: ve ampoules (400 units/mL): £352

Further reading

1. Martinez-Zapata MJ, Roqué i Figuls M, Català E, et al. Calcitonin for metastatic bone pain. Cochrane Database Syst Rev 2006;3:CD003223
2. Schug SA, Palmer GM, Scott DA, et al. Acute Pain Management: Scienti c Evidence. 4th edition, 2015. Melbourne: Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine

13.5 Cannabis

Introduction

Natural cannabis products are illegal in most countries worldwide

The prevalence of cannabis use in patients attending chronic pain clinics is approximately 12–15%

Compounds are derived from *Cannabis sativa*, *Cannabis ruderalis*, and *Cannabis indica* species

Natural preparations contain over 100 metabolically active compounds, including:

- THC
- CBD
- Cannabinol (CBN)
- Cannabigerol (CBG)
- Tetrahydrocannabivarin (THCV)
- Non-cannabinoid compounds

Indications

The evidence to support the e cacy, tolerability, and safety pro le of cannabinoids in the treatment of acute and chronic pain is currently limited

Nonetheless, cannabinoids may be considered in highly selected patients after failure of multiple pharmacological and non-pharmacological therapies for the following conditions:

- CNCP: neuropathic pain or spasticity-related pain in MS
- Chemotherapy-induced nausea and vomiting (CINV)
- Palliative care: appetite stimulation, weight gain, antiemesis, analgesia
- Paediatric epilepsy
- Other conditions in which it has been used: Parkinson's disease, anxiety disorder, bromyalgia, PTSD, sleep disorders, Tourette's syndrome

Analgesic e cacy

A meta-analysis (including 104 studies, 47 RCTs, and 9958 participants) on the e ectiveness of cannabinoids in CNCP of mixed aetiology showed:

- NNT for 30% pain reduction: 24 (95% CI 15–61)
- NNH: 6 (95% CI 5–8)
- No signi cant impacts on physical or emotional functioning; low-quality evidence of improved sleep and patient global impression of change

Currently no strong support for use in CNCP, due to lack of robust evidence

Cannabis-based medications and licensed indications

Natural cannabis products:

- Nabiximols (Sativex®): THC:CBD ratio 1:1—MS and intractable cancer pain
- Whole plant extract (Cannador®): plant-based, THC:CBD ratio 2:1—no licensed indications

Synthetic preparations:

- Nabilone (Cesamet®, Canemes®): synthetic THC—CINV
- Rimonabant (Acomplia®): CB1 receptor inverse agonist and mu opioid receptor antagonist—licensed for obesity and smoking cessation. Withdrawn in Europe in 2008 due to mental health adverse e ects
- Dronabinol (Marinol®): synthetic THC—CINV
- Synthetic CBD (Subsys®): synthetic CBD—intractable cancer pain

Mechanism of action

Endocannabinoid system agonism implicated for analgesia in in ammatory and neuropathic pain states

Anandamide and *2-arachidonoylglycerol* are the two major endocannabinoids derived from membrane phospholipids

Cannabinoids bind to cannabinoid GPCRs, causing membrane hyperpolarization and inhibition of NT release. Main features of the endocannabinoid system include:

- Cannabinoid receptor type 1:
  - Mainly CNS (PAG, RVM, thalamus), but also peripheral neuronal tissues at pre-synaptic sympathetic nerves
  - Involved in modulation of the NTs ACh, dopamine, GABA, D-aspartate, cholecystokinin, glutamate, serotonin, and noradrenaline
  - Involved in pain perception, movement, brain reward/addiction, mood, and cognition systems
- Cannabinoid receptor type 2:
  - Mainly in the peripheral immune system (macrophages, lymphocytes, natural killer cells, mast cells), but also in glial cells of the CNS
  - Inhibition of release of pro-in ammatory cytokines and movement of immune cells

Cannabinoid system also modulates:

Ascending nociceptive and descending anti-nociceptive pathways in the spinal cord and higher relay centres

A erent sensitization in the peripheral nervous system

Routes of administration and dosing

PO, sublingual, inhaled, topical

Titration period followed by maintenance therapy

Nabiximols (Sativex®): oro-mucosal spray containing THC 2.7 mg and CBD 2.5 mg per 100 microlitres spray (maximum 16 doses daily)

Whole plant extract (Cannador®): THC 2.5 g and CBD 1.2 mg per oral capsule

Dronabinol (Marinol®): 2.5/5/10 mg oral capsule. Maximum dose 20 mg daily

Nabilone (Cesamet®): 0.25/0.5/1 mg oral capsule. Maximum dose 6 mg daily

Pharmacokinetics

Absorption:

Depends on route and highly variable between patients

Inhaled (smoking, vaporizers): rapid onset of action, bioavailability of around 18%, levels falling within 2 hours, inaccurate dosing

Oral: poor absorption, low bioavailability, di cult to titrate

Sublingual: Sativex® (spay) achieves peak plasma levels in 45–120 minutes

Distribution: highly lipophilic, high protein binding, accumulates in fatty tissues

Metabolism: THC and CBD are metabolized by CYP450 enzymes

Excretion: faeces (majority) and renal. Long elimination t1/2 of 24–36 hours due to high lipid solubility

Pharmacodynamics

Nervous system: psychoactive properties (THC as primary psychoactive component), sedation, anxiolysis, analgesia

GI: appetite stimulant, antiemetic

Immunological: in ammatory cytokine inhibitor

Contraindications

Unstable ischaemic heart disease (IHD) or arrhythmias

Severe renal or hepatic disease

Active mental health disorder, especially psychosis, family history of psychosis, history or risk of aberrant drug behaviour

Co-administered sedatives, including alcohol

Adverse e ects

Low acute toxicity in commercially prepared drugs. The higher the frequency, dose, and duration of use, the more likely adverse e ects

Nervous system: dizziness, sedation, dry mouth, dysphoria, impaired cognition and memory

Use in younger age (<25 years old) associated with:

Reduction in frontal and parietal brain lobe volumes

Poorer educational achievements, lower IQ

Precipitation of the onset of mental health disorders, poorer treatment compliance, and increased hospitalization rates and risk of self-harm

Cardiovascular: hypo- and hypertension, tachy- and bradycardia

Respiratory: if smoked, associated e ects of additional compounds of tobacco

Endocrine: lowers testosterone levels and quality/number of sperm

Mental health: hallucinations, psychosis, depression, anxiety, mania, self-harm, strong relationship between schizophrenia and cannabis use

Drug and alcohol: cannabis dependence syndrome (10%)

Interactions

Inhibition of cytochrome P450 isoenzymes, including CYP2D6 and CYP3A4

Further reading

1. Mücke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018;3:CD012182
2. Raja S, Sommer C. Pain 2014 Refresher Courses. Treatment of neuropathic pain: opioids, cannabinoids, and topical agents. 15th World Congress on Pain, 2014. Seattle, WA: IASP Press
3. Stockings E, Campbell G, Hall W, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions. Pain 2018;159(10):1932–54

13.6 Capsaicin

Class of drugs

Extract from chilli peppers belonging to the *Solanaceae* family

Formulations and brand names (pricing)

Zacin® 0.025% topical cream—250 mcg/g (45 g: £17.71)

Axsain® 0.075% topical cream—750 mcg/g (45 g: £14.58)

Qutenza® 8% patch—179 mg per patch (£210.00 per patch)

Pharmacodynamics—mechanism of action

Action of capsaicin on Transient Receptor Potential Vanilloid (TRPV)

Receptor on C- bres

TRPV1 is a ligand-gated non-selective cation channel of the TRP family that could be activated by a variety of noxious stimuli

Chronic exposure to capsaicin rst stimulates, then desensitizes this channel to noxious stimuli, including capsaicin (tolerance develops with chronic use)

Local depletion of substance P

As Substance P is depleted, there is inadequate chemical stimulus available to activate C- bres

Pharmacokinetics

Minimal systemic absorption from skin

Can be excreted in breast milk if the 8% patch is used

Can stimulate bradykinin release

Indications

OA, PHN, painful diabetic neuropathy

Qutenza® (8% patch) is licensed by the FDA only for PHN (the only other topical product licensed for PHN is 5% lidocaine plaster)

Unlicensed use: back pain, painful diabetic neuropathy, some forms of refractory pruritus

Contraindications/cautions

Broken skin, active ulceration (for both the patient and the individual applying the medication!)

Avoid: contact with eyes, hot shower or bath just before or after application, inhalation of capsaicin vapour

Not to be used under tight bandages

Caution as capsaicin can increase cough, especially in patients on ACEIs (due to its agonist action on TRPV present in the respiratory tract)

Note: only wear nitrile gloves for application since latex does *not* provide protection from capsaicin!

Caution in patients with hypertension as capsaicin could accentuate hypertension, and rarely accentuate AV nodal block

Application of Qutenza® patches

Qutenza® (8% patch) could be applied every 12 weeks—a single patch is applied for up to 30–60 minutes

Prepare the a ected area by mapping the painful area, then apply LA topically or use oral analgesic (e.g. tramadol 50–100 mg) to reduce the intense burning sensation

Up to a maximum of four patches is recommended per application

Side e ects

Most common is severe skin burning (if not premedicated with adequate topical LA)—treated by short-acting opioids, and by application of ice to the a ected area

Nausea is rare, transient increase of blood pressure

Special circumstances

Safe in patients with hepatic or renal impairment

Not licensed for use in patients younger than 18 years

Caution in breastfeeding women since capsaicin has been isolated from milk (in rats)

Additional information

Use nitrile gloves for application of capsaicin

Evaluate the patient for uncontrolled hypertension or chronic cough before considering capsaicin treatment (relative contraindication)

Avoid contact with mucous membranes—wash hands thoroughly

Disposal of unused patches and used products in biohazard dispensers as per local policy (could be an irritant to those who come into contact if disposed of in regular clinical waste)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Smith HS, Pappagallo M, Stahl SM (eds). Essential Pain Pharmacology: The Prescriber's Guide. 1st edition, 2012. Cambridge: Cambridge University Press
3. Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th edition, 2017. New York, NY: McGraw-Hill

13.7 Clonazepam

Class of drugs

Benzodiazepine (BZD)

Indications

Epilepsy
Myoclonus
Panic disorder
Movement disorder (akathisia)
Insomnia
Muscle spasticity
Not recommended for treating neuropathic pain

Contraindications

Respiratory depression and acute pulmonary insu ciency
Marked neuromuscular respiratory weakness, including unstable myasthenia gravis
Alcohol or recreational drug abuse

Dose

Initial dose 1 mg daily for 3–4 days and increased according to response over 2–4 weeks, to a usual maintenance dose of 4–8 mg in 3–4 divided doses
Children:

- <1 year: initially 250 mcg, which can be increased to 0.5–1 mg daily
- 1–5 years: initially 250 mcg, which can be increased to 1–3 mg daily
- 5–12 years: initially 500 mcg, which can be increased to 3–6 mg

Caution in hepatic and renal impairment
Patients can develop coma due to increased cerebral sensitivity. Where necessary, BZDs with shorter t1/2 should be used
Avoid long-term use due to its S/Es and contraindications

Mode of action

Structurally a 1,4-BZD. Its primary mode of action is to facilitate GABAergic transmission in the brain by a direct e ect on GABA receptors, by inhibiting ring of raphe cells which are located in the midbrain and pons

Side e ects

Common: respiratory depression, drowsiness, dizziness, cognitive impairment, headaches, sleep disturbances, slurred speech, dry mouth, constipation, and blurred vision. Can worsen depression

Occasional: dysphoria and blood disorders

Very rare: psychosis and suicidal ideations; although the mechanism underlying these risks is not known, available data do not exclude the possibility of increased risk either (therefore, the patient's mental state should be monitored)

Pharmacokinetics

Absorption: oral bioavailability of 90%, with peak concentrations reached within 1–4 hours of oral administration

Distribution: 85% protein-bound

Metabolism: highly metabolized before undergoing acetylation, hydroxylation, and glucuronidation

Excretion: <2% in the urine

Interactions

Reduced plasma concentration when given with carbamazepine and phenytoin

Increased risk of neurotoxicity when given with lithium

Increased risk of S/Es when given with sodium valproate

Increased sedative e ects when given with TCAs, antipsychotics, opioids, or other sedatives

Special circumstances

Special precaution in the elderly with the dose initiated at 500 mcg and titrated very cautiously to higher doses

The safety pro le in pregnancy is less clear. Some inconclusive data associate its intake during pregnancy with cardiac and facial malformations. If BZDs are necessary, chlordiazepoxide and diazepam may be safer options

Additional information

Drowsiness caused by clonazepam may a ect performance of skilled tasks (e.g. driving, use of machinery)

Current limitations of point-of-care immunoassays suggest testing by mass spectrometry to ensure better accuracy

Avoid long-term use to mitigate the risk of development of dependence and S/Es listed above

Cost

Clonazepam 500 mcg (100 tablets): £31.67

Clonazepam 2 mg (100 tablets): £34.33

Monthly cost for 0.5–1 mg/day: £9.50–19

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Corrigan R, Derry S, Wi en PJ, Moore RA. Clonazepam for neuropathic pain and bromyalgia in adults. Cochrane Database Syst Rev 2012;5:CD009486.

13.8 Clonidine

Class of drugs

Centrally acting -2 adrenergic agonist which reduces sympathetic out ow

Indications

Management of alcohol, opioid, and nicotine withdrawal symptoms

Hot ushes and excessive sweating in menopause

Migraine prophylaxis

Prevention and management of anxiety and delirium (e.g. after surgery, critical ill patients etc.)

Acute pain:

- Not a rst line agent in acute pain management due to associated S/Es and other agents are more e ective for acute pain management
- E ective adjunct to opioid-tolerant patients and in complex acute pain predominantly due to its anxiolytic e ects
- Neuraxial blockade (intrathecal, epidural): as an adjunct to LAs, clonidine improves the duration of analgesia, reduces systemic use of opioids, and prolongs the time needed until rst-rescue analgesia
- Peripheral regional blockade and perineural infusions: improves duration of action of analgesia and anaesthesia
- Weak evidence to support the use of clonidine for intra-articular use (knee arthroscopy) and surgical site in ltration following mastectomy

Chronic pain:

- *Neuropathic pain:*
  - Diabetic neuropathy: topical clonidine may provide some bene t
  - At level of neuropathic pain in SCI: intrathecal clonidine and morphine have proven to be useful
  - Intractable cancer neuropathic pain: neuroaxial clonidine can be useful
- CRPS: epidural or topical clonidine may provide pain relief in refractory cases
- Pain from muscular spasticity: can reduce pain from muscle spasms
- Chronic post-surgical pain—weak evidence demonstrates that epidural clonidine and steroid may improve pain relief and sleep in post-thoracotomy pain

Caution

Avoid in patients with hypotension, bradycardia, sedation, or cognitive dysfunction, and those at risk of falls

Severe renal impairment: reduce dosage

Dose

PO 50–600 mcg in divided doses

IV 50–300 mcg in divided doses

Neuraxial 15–30 mcg

Mode of action

Activates -2 (pre-synaptic) receptors in the brain, DH of the spinal cord, DRG, and sensory neurons. It reduces noradrenaline release and sympathetic out ow at both central and peripheral adrenergic terminals, causing sedation, anxiolysis, reduction in anaesthetic requirement, and gastric motility

Anti-nociceptive action:

DH of the spinal cord: reduces the release of noradrenaline and enhances the action of descending inhibitory pathways

Peripheral sensory neuron terminals: blocks adrenergic receptors (-1, -2) expressed on sensory neurons or on post-ganglionic sympathetic terminals following a nerve injury

Imidazoline receptor agonist: activation causes analgesia. These receptors are located in the brain, spinal cord, and peripheral nerve endings

Clonidine has the intrinsic ability to block C- and A-delta bres

Causes local vasoconstriction and may prolong the duration of LAs

Side e ects

Common: hypotension, bradycardia, sedation, dry mouth, and rebound hypertension

If used over a prolonged period, it may cause withdrawal symptoms if stopped abruptly

Pharmacokinetics

Oral bioavailability: 75–95%

Onset of action: 30–60 minutes; peak plasma levels: 1–3 hours

Elimination t1/2: 6–26 hours

Excretion: 60–65% excreted unchanged in the urine

Interactions

Antiepileptics, alcohol, sedatives, and anxiolytics: potentiates sedative and depressant e ects

Digoxin: may worsen arrhythmias

Special circumstances

Avoid in pregnancy and lactation: crosses the placental barrier, secreted in breast milk

Avoid long-term use in children

Cost

Oral 25 mcg, 112 tablets: £4

Oral 100 mcg, 100 tablets: £8

Oral 10 mcg/mL 100 mL bottle: £68

Further reading

1. Campbell CM, Kipnes MS, Stouch BC, et al. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain 2012;153:1815–23
2. Kumar A, Maitra S, Khanna P, et al. Clonidine for management of chronic pain: a brief review of the current evidences. Saudi J Anaesth 2014;8(1):92–6

13.9 Contrast agents

Introduction

Contrast agents have been used in pain management practice to ensure correct positioning of the needle tip, to con rm the intended target, to identify intravascular uptake, and to distinguish between di erent anatomical structures

This facilitates the deposition of diagnostic/therapeutic agents near the targeted area

Classi cation

(See Table 13.9.1.)

Broadly, radiocontrast agents can be divided into either positive (these agents absorb X-ray to produce darker shadows of tissues in question) or negative (transparent to X-ray)

Positive contrast agents are commonly used, as they are radio-opaque. They can also be divided into iodinated and non-iodinated agents (gadolinium-based)

Iodinated agents are commonly used and they are divided into ionic and non-ionic agents, based on water solubility and charge of the iodinated molecule. They can be monomers or dimers (based on molecular structure) and can also be classi ed based on osmolality

Omnipaque™ 240 contains 240 mg/mL of organic iodine
Omnipaque™ 300 contains 300 mg/mL of organic iodine
Niopam® 200 contains 200 mg/mL of organic iodine

Indications

Intravascular: digital subtraction angiography (DSA), CT angiography
Intrathecal: myelography
Others: discogram, epiduroscopy, arthrography, nerve root/ganglion/plexus identi cation
Enteral: GI problems

Contraindications

Known allergy to contrast agents or allergy to iodine

Dose

Varies depending on the procedure (from a few mL to a few hundred mL)
Use the lowest dose possible. For simple pain interventions, usually 1–3 mL of contrast is su cient

Mechanism of action

Iodine is responsible for causing radio-opacity in iodinated contrast agents and it outlines the structures better when there exists a density di erence between the structures

Table 13.9.1 Types of radiocontrast agents

Iodinated	Ionic (charged particles)	Non-ionic
Monomer	Osmolality—high Viscosity—low Examples: diatrizoate (Uorgra n®), iothalamate (Conray®)	Osmolality—low to intermediate Viscosity—intermediate Iohexol (Omnipaque™) Iopamidol (Niopam®) Both licensed for intrathecal use as non-ionic Commonly used in pain interventions
Dimer	Osmolality—intermediate Viscosity—intermediate Example: ioxaglate (Hexabrix®)	Osmolality—low Viscosity—highest Example: iotrolan (Isovist®)

Relevant pharmacokinetics/pharmacodynamics

Contrast agents share a tri-iodinated benzene ring structure

The t1/2 of redistribution of the intravascular compartment is between 2 and 5 minutes and equivalent to that of the extracellular uid. Contrast agents are carried free in plasma

Serum protein binding is <5%

There is no evidence of biotransformation of these agents and elimination is almost entirely through the kidneys

Adverse reactions

Idiosyncratic anaphylactoid—self-limiting minor adverse events, such as pain and rash, to life-threatening reactions

Dose-dependent reactions—cardiac S/Es, seizures, nephropathy. Uncommon with simple pain interventions if non-vascular injections and small doses used

Higher risk of adverse e ects with high osmolar and ionic agents

Risk factors for adverse reactions

History of previous reaction, allergy, asthma, dehydration, pre-existing renal disease, sickle cell anaemia, polycythaemia, myeloma, and use of NSAIDs

Interactions

Contrast agents themselves do not directly interact with other agents. However, caution must be exercised with Omnipaque™ in patients with a history of epilepsy, renal disease, chronic alcoholism, and MS

Niopam can a ect iodine uptake by thyroid tissue more than Omnipaque™ can, and should be used cautiously in hyperthyroid patients

Special circumstances

There are no studies on use of Omnipaque™ in pregnant women. It is advisable to supplement breastfeeding with bottle feeding following Omnipaque™ use for 24 hours, as contrast agents are excreted unchanged in breast milk

Additional information

Drugs which lower the seizure threshold, especially phenothiazine-based antihistamines and antiemetics, are not recommended to be used along with Omnipaque™

Contrast agents are nearly twice more viscous at 20°C than at body temperature

Warming the contrast agents can o er better ow rates in angiography as viscosity decreases

Further reading

1. Beckett KR, Moriarity AK, Langer JM. Safe use of contrast media: What the radiologist needs to know. RadioGraphics 2015 35:6:1738–1750
2. Rathmell, James P. Radiographic contrast agents. In: Rathmell JP (ed). Atlas of Image-Guided Intervention in Regional Anesthesia and Pain Medicine. 2006; pp. 16–22. Philadelphia, PA: Lippincott Williams and Wilkins

13.10 Hyaluronidase

Class of drugs

Enzyme used to render tissues more readily permeable to injected uids

Indications—licensed uses

Enhances permeation of SC or IM injections
Enhances permeation of LAs
Enhances permeation of ophthalmic LAs
Hypodermoclysis (introduction of uids by SC infusion)
Extravasation: in ltrate as soon as possible into the a ected area
Haematoma: in ltrate into the a ected area

Contraindications

Avoid sites where infection/malignancy present
Corneal application, IV administration
In anaesthesia in premature labour
To enhance absorption and dispersion of dopamine and/or adrenoceptor agonists
To reduce swelling of bites/stings

Caution

Elderly: control speed and total volume; of administration avoid overhydration, especially in renal impairment

Dose

SC/IM/local in ltration: 1500 units to be dissolved directly into the solution to be injected (check compatibility)
Some use up to 3000 units per injection (for epidural adhesiolysis)
To the eye: 15 units/mL mixed with LA solution for ophthalmic block
Hypodermoclysis/extravasation/haematoma: dissolve 1500 units in 1 mL of water/0.9% saline

Mode of action

Reversibly depolymerizes hyaluronic acid, a polysaccharide present in connective tissue, increasing tissue permeability
Hyaluronidase as adjuvant to epidural steroid increases its e cacy and duration of action by reducing brosis and oedema in tissues and lysing the adhesions, thus facilitating the spread of the injected substance

Monitoring of treatment

No additional monitoring required beyond that in place for procedure

Side e ects

Common: oedema
Rare: bleeding, bruising, infection, local irritation
Frequency not known: anaphylaxis, severe allergy

Interactions

With aspirin or dexamethasone (larger amounts of hyaluronidase may be required)

Special circumstances

Pregnancy: caution
Breastfeeding: caution

Additional information

Store refrigerated at 2–8°C

Cost

Hyaluronidase 1500-unit powder for injection: £13.65/ampoule

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Yentis S, Hirsch N, Smith G. Anaesthesia and Intensive Care A–Z. 6th edition, 2018. Edinburgh: Elsevier
3. Menzel EJ, Farr C. Hyaluronidase and its substrate hyaluronan: biochemistry, biological activities and therapeutic uses. Cancer Lett 1998;131:3–11

13.11 Ketamine

Class of drugs

Ketamine is a water-soluble aryl-cyclo-alkylamine and is structurally related to cyclidines

Indications

Anaesthetic induction agent, especially suitable for patients who are cardiovascularly unstable
Sole anaesthetic agent for short procedures such as burns dressing
Potent perioperative analgesic at sub-anaesthetic doses
Opioid-sparing e ect
As third-line agent in resistant pain conditions, particularly with a neuropathic component (CRPS type 1, PHN, orofacial pain, and phantom limb pain)
Third-line drug in opioid- and adjunct-resistant cancer pain
New evidence emerging on its role as an antidepressant

Contraindications

Malignant hypertension, certain heart conditions, raised ICP, eclampsia, psychiatric conditions

Routes of administration

IV, IM, PO, nasal, rectal, and intrathecal routes

Dose

Anaesthetic: 1.5–2 mg/kg IV; 10 mg/kg IM with onset time 2–8 minutes

Acute pain: 0.1–0.5 mg/kg IV bolus dose and 0.05–0.2 mg/kg/hour continued as IV infusion

Chronic pain: 10–40 mg four times daily PO, titrate according to individual. Ketamine infusion can be done for neuropathic pain as a day case procedure at 0.15–0.3 mg/kg over 30 minutes

Cancer: racemic ketamine 1 mg/kg/day or S (+) ketamine (0.5–2 mg/kg/24 hours) infusion up to 600 mg/day as an IV infusion, 67.2 mg/day via intrathecal route

Palliative: PO doses of 50–100 mg four times daily have been used

Mechanism of action

Primarily acts as non-competitive antagonist at NMDA receptor Ca^{2+} channel pore which can counteract wind-up or central sensitization

Agonist at and adrenergic receptors

Antagonistic e ect at CNS muscarinic receptors

Monitoring

Repeated ketamine administration may require careful liver enzyme monitoring

Adverse e ects

CNS: drowsiness, nausea and vomiting, visual/auditory hallucinations, paranoid e ects, anxiety, and euphoria

CVS: direct negative inotropic e ect (high-dose infusion) and indirect stimulatory e ect (low-dose infusion). Ketamine causes tachycardia, increases systemic and pulmonary hypertension, and increases cardiac output and myocardial oxygen consumption

Hepatic: reversible hepatic enzyme elevation

Renal: both upper and lower renal tract symptoms may occur. Ketamine-induced uropathy includes complex changes in the bladder and upper urinary tract changes. Regular and prolonged use of high doses may lead to cystitis (limit dose to <160 mg/day)

GI tract: causes upper GI symptoms, including nausea, GI bleeding, and anaemia

Relevant pharmacodynamics/pharmacokinetics

Ketamine molecule is freely water-soluble, with a molecular weight of 238 g/mol. Its pKa is 7.5

It is formulated as a slightly acidic aqueous solution (pH 3.5–5.5)

Ketalar® is a racemic mixture of equal proportions of two enantiomers

The active S (+) enantiomer is stronger than both racemic (twice) and R ( ) enantiomer (four times)

Due to high lipid solubility, it has extensive distribution. Vd ranges from 1.5 to 3.2 L/kg. It has low protein binding between 10% and 30%

High lipid solubility and low plasma binding facilitate rapid transfer across the BBB

Extensive rst-pass metabolism, hence poor oral bioavailability of 15%—the predominant route of metabolism is via the liver involving N-demethylation and producing norketamine. Norketamine has nearly one-third the anaesthetic potency, as well as analgesic properties

Conjugated metabolites are excreted mainly via the renal route

Interactions

Ketamine and norketamine are metabolized by the CYP450 family

Opioids, alcohol, sedatives, anxiolytics potentiate the depressant e ects

Special circumstances

Ketamine in sub-anaesthetic doses may adversely a ect pregnancy outcomes (based on animal studies)

Additional information

Oral ketamine has limited shelf life. Controlled drug; although inexpensive, ketamine prescription is resource-intensive and needs regular monitoring and repeat prescriptions

Potential for drug abuse, so avoid in vulnerable patients

Cost

Ketamine for injection—200 mg/20 mL one vial: £5 (£50 for ten vials)

Ketamine for injection—500 mg/10 mL one vial: £8.80 (£70 for ten vials)

Further reading

1. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. Pharmacol Rev 2018;70(3):621–62
2. Expert Committee on Drug Dependence. Ketamine—update review report. 2014. Geneva: World Health Organization

13.12 Methocarbamol

Introduction

Central muscle relaxant indicated for treating skeletal muscle spasms

Alternative to baclofen/diazepam in pain medicine

Mechanism of action

Unclear, but may cause inhibition of carbonic anhydrase and CNS depression. It may decrease nerve transmission at the spinal and supraspinal levels and also prolong the refractory period of muscle cells

Dose

Initial dosage: 1500 mg four times daily, initially for 2–3 days, Maintenance: PO 750 mg 4-hourly, and then 1500 mg three times daily or 1000 mg four times daily. Maximum: 4 g/day

Each tablet contains 750 mg and the injectable solution has 100 mg/mL

Methods of administration: PO/IV/IM

Uses

Skeletal muscle spasm associated with acute musculoskeletal pain

Parenteral: 1 g IV/IM; additional doses three times daily; not to exceed 3 g/day

Enteral dose: 1500 mg PO four times daily for 48–72 hours; no more than 8 g/day and reduce to 4–4.5 g/day in divided doses

Tetanus

Adjunct therapy: initially 1–2 g IV injection (at 300 mg/min), up to a total dose of 3 g; may repeat 1–2 g IV 6-hourly until PO tolerated; total 24 g PO

IM administration: not to exceed 500 mg (5 mL undiluted)

Pharmacokinetics

Rapidly absorbed PO, with high therapeutic index

Onset 30 minutes; peak serum levels 1–2 hours; peak plasma concentration: 16–30 mcg/mL

Protein binding: 46–50%

Metabolism: conjugation, dealkylation, and hydroxylation

Metabolites: glucuronide and sulphate conjugates of 3-(2-hydroxyphenoxy)-1,2-propanediol-1-carbamate and 3-(4-hydroxy-2-methoxyphenoxy)-1,2-propanediol-1-carbamate

Elimination t1/2: 0.9–1.8 hours

Duration of treatment

Depends on symptoms but should not exceed 30 days

Side e ects

Common: dizziness, headache, light-headedness, mild sedation

Nausea and vomiting, dyspepsia, metallic taste, jaundice

Rare: fever, angio-oedema, hypersensitive reactions, conjunctivitis, nasal congestion, ushing, bradycardia, syncope

Very rare: blurred vision, drowsiness, tremor, convulsion, restlessness, anxiety, confusion, anorexia, leucopenia, anaphylaxis

Contraindications

Hypersensitivity, coma or pre-coma states, brain injury or epilepsy

Myasthenia gravis

Interactions

May potentiate CNS depressant e ects with opioids, BZDs, antihistamines, antipsychotics (clozapine), and antidepressants (mirtazapine)

Caution

In renal impairment, **avoid parenteral** form due to the presence of PEG

May change the colour of urine to brown, black, or green

Drivers and machine operators to be warned as CNS depressant

Drug overdose—seizures, coma, and fatality with supportive treatment

Abuse potential is less

Special circumstances

Pregnancy—Category C (use only if bene ts outweigh risks)

Lactation: unknown if it is excreted in breast milk

Elderly—halve the dose

Hepatic impairment—t1/2 elimination is prolonged; hence, increase the dosing interval

Children—safety and e cacy not been established

Additional information

In the emergency department, patients with acute, non-traumatic, non-radicular low back pain, combining naproxen with methocarbamol did not improve functional outcomes, compared with naproxen + placebo

Cost

750 mg 100 tablets: £12.65 (monthly cost for 1.5–4 g/day: approximately £7–25)

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. Electronic Medicines Compendium. Methocarbamol. https://www.medicines.org.uk/emc/search?q=methocarbamol
3. Medscape. https://reference.medscape.com
4. Witenko C, Moorman-Li R, Motycka C, et al. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. P T 2014;39(6):427–435

13.13 Methoxy urane

Introduction

Introduced in early 1960s, as a low-dose self-administered analgesic, but was withdrawn in 2005 due to safety reasons

Re-emerged in 2015 as Penthrox®

Used in Australia for >40 years for trauma-related pain and procedural pain in children and adults

Name

Penthrox® 99.9% (999 mg per 1 g)

Class of drugs

Fluorinated hydrocarbon group of volatile anaesthetic agents

Presentation

Each bottle contains 3 mL of volatile liquid

Clear, almost colourless, characteristic fruity odour

Indications

Emergency relief of moderate to severe pain in conscious adults with trauma and related pain

Outpatient medical and surgical procedures, including colonoscopy, changes in burns dressings, and prostate biopsies (Australasia)

Contraindications/caution

Hypersensitivity

Malignant hyperthermia

Clinically signi cant cardiovascular instability, respiratory depression, and altered consciousness

Renal impairment:

Causes signi cant nephrotoxicity at high doses (serum levels >40 micromoles/L)

Liver impairment:

Previous halogenated hydrocarbon anaesthesia, especially if within 3 months, may increase potential for hepatic injury

Not appropriate for breakthrough pain in chronic pain conditions or in trauma pain in closely repeated episodes

Occupational exposure: use with activated carbon (AC) chamber which adsorbs exhaled methoxy urane

Routes of administration and dosing

Self-administered under supervision

Handheld Penthrox® inhaler, custom-built

One 3 mL bottle is a single dose; second bottle only where needed

Recommended dosing schedule: no more than 6 mL in a single day; administration on consecutive days not recommended; total weekly dose should not exceed 15 mL

Mode of action

Mechanism of analgesic action not fully elucidated

Onset is rapid; 6–10 inhalations and then inhale intermittently to maintain analgesia (self-titrate)

Duration of action: continuous inhalation of 3 mL bottle—analgesia for up to 25–30 minutes

Side e ects (limited by nature of self-administration)

Hypotension and bradycardia. Not signi cant at analgesic doses

Sedation, dizziness, euphoria, reduced concentration, headache, restlessness, mood changes

Cough, hypoxia, dry mouth, nausea, vomiting

Hepatic and renal failure

Pharmacokinetics

Absorption:

Enters the lungs as vapour; rapidly transported into blood—therefore, rapid onset of analgesic action

Distribution:

Highly lipophilic, di uses into adipose tissue → reservoir, slowly released over days

Metabolism:

Hepatic—dichlorination and O-demethylation, mediated by CYP450, metabolized to free uoride and oxalic acid which are responsible for renal damage

Elimination:

Approximately 60% excreted in the urine as organic uorine, uoride, and oxalic acid

Remainder exhaled unaltered or as CO_2

Interactions

No reported drug interactions when used at analgesic doses (3–6 mL)

Hepatic enzyme inducers—potential toxicity

Avoid with concurrent use of nephrotoxic drugs

Avoid using sevo urane following methoxy urane analgesia; sevo urane increases serum uoride levels

Additive depressant e ects with CNS depressants

Special circumstances

Children: not for use in those aged <18 years

Renal and hepatic impairment: caution

Pregnancy: animal studies—no observed harmful e ects

Obstetric analgesia—single report of neonatal respiratory depression associated with a high fetal level of methoxy urane

Breastfeeding: insu cient data on excretion in human milk

Ability to drive/operate machinery: minor in uence

Additional information

No clear evidence of carcinogenic or mutagenic properties

Does not a ect sperm cells in mice

Crosses the placenta in animal studies, but no evidence of embryotoxic or teratogenic properties

Delayed fetal development was observed with repeated dosing

Cost

Vapour 3 mL bottle: £17.89

Further reading

1. Porter K, Dayan AD, Middleton PM. The role of inhaled methoxy urane in acute pain management. Open Access Emerg Med 2018;10:149–64
2. Jephcott C, Grummet J, Nguyen N, et al. A review of the safety and e cacy of inhaled methoxy urane as an analgesic for outpatient procedures. Br J Anaesth 2018;120(5):1040–8
3. Electronic Medicines Compendium. https://www.medicines.org.uk/emc

13.14 Nitrous oxide

N_2O is an inhalation anaesthetic agent which was rst extracted in 1772 by Joseph Priestley and was further developed for analgesia by H. Davy (1799)

Chemical properties

At room temperature, it is colourless and non- ammable but supports combustion

Sweet taste and odour, soluble in water

Stored in French blue cylinders as a liquid

Preparation: ammonium nitrate (NH_4NO_3) → 2 H_2O + N_2O

Weak general anaesthetic properties, used mainly as a carrier gas with volatile inhalational agents

Minimum alveolar concentration (MAC)—105

Low blood/gas partition coe cient of 0.46—rapid onset of action

The lling ratio is 0.75, and critical temperature 36.5°C

Pharmacokinetics

Kinetics—administered by inhalation and absorbed by di usion through the lungs; eliminated via respiration (<0.004% metabolized)

Elimination t1/2: 5 minutes

Uses

Analgesic and CNS depressant

General anaesthesia as a N_2O and oxygen mixture—70%:30%, respectively

Entonox®: 50:50 (N_2O:oxygen) in dental surgery, in obstetrics for labour analgesia, and for procedural pain, e.g. change of burns dressing

In the UK, the maximum permissible level is 100 ppm

Mechanism of action

Exact mechanism is unclear but may act on GABA and glycine receptors and ligand-gated ion channels which are mainly inhibitory

E ects

Mild depressant e ects on the myocardium, increased sympathetic activity

Mild decrease in respiratory T_V and increased RR

Increases cerebral blood ow

Demonstrates concentration e ect and second gas e ect

Side e ects

Nausea, vomiting

Prolonged use (>6 hours) interferes with methionine synthesis and decreases thymidine and DNA synthesis

May cause megaloblastic anaemia and peripheral neuropathy due to vitamin B12 de ciency

Interactions

Potentiates hypotension with amitriptyline and antihypertensives (-blockers, diuretics, ACEIs)

CNS depression with sedatives, alcohol, and CNS depressants (BZDs, gabapentinoids)

Potential for abuse

N_2O is not a controlled drug (second most popular recreational drug amongst young people)

Environmental e ects: contributes to greenhouse gas e ects, global warming, and ozone layer depletion

Contraindications

Expands air spaces (contraindicated in patients with pneumothorax, ocular surgery using intraocular gas, intestinal obstruction, etc.)

Special circumstances

Pregnancy—may a ect fertility and fetal development after exposure to high concentrations for prolonged periods

May depress neonatal respiration

Applications of N_2O/research of N_2O in pain medicine

The analgesic e ects of N_2O may be linked to interactions between endogenous opioids and the descending noradrenergic system

NMDA antagonism of N_2O may o er a signi cant bene t in the reduction of chronic post-surgical pain and OIH

N_2O is as e cient as, and safer than, various other analgesic methods used during colonoscopy procedures, but further trials are necessary

The ENIGMA-II trial showed that N_2O does not increase the risk of death or cardiovascular complications (note: ENIGMA-I trial: N_2O was associated with an increased long-term risk of MI, but not of death or stroke)

Further reading

1. Leslie K, Myles PS, Chan MT, et al. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. Anesth Analg 2011;112(2):387–93
2. Chan MT, Wan AC, Gin T, et al. Chronic postsurgical pain after nitrous oxide anesthesia. Pain 2011;152(11):2514–20

13.15 Orphenadrine

Name, class of drugs

Orphenadrine oral solution (50 mg/5 mL)

Anti-Parkinson medication (anti-muscarinic)

Indications

Parkinsonism

Drug-induced extrapyramidal symptoms

Unlicensed for nociceptive MSK pain symptoms

May also reduce tremor and rigidity

Contraindications

Acute porphyrias

GI obstruction

Myasthenia gravis

Caution in cardiovascular disease, the elderly, hypertension, angle closure glaucoma, prostatic hypertrophy, psychotic disorders, and pyrexia

Dose

Orphenadrine 50 mg three times daily (in combination with paracetamol 1 g three times daily)

Orphenadrine may be increased in steps of 50 mg every 2–3 days according to response

Usual daily dose: 150–300 mg
Maximum daily dose: 400 mg
Reduced dose in renal and liver failure

Mode of action

Post-ganglionic anticholinergic, antihistaminergic, and LA properties
CNS depressant with skeletal muscle relaxant e ects (precise mechanism of action not known)
Does not directly relax skeletal muscle
Therapeutic action may be related to analgesic properties
May reduce skeletal muscle spasm (possibly through an atropine-like central action on cerebral motor centres or on the medulla)

Side e ects

Constipation, dry mouth, nausea, vomiting, tachycardia, dizziness, sedation, confusion, euphoria, hallucinations, impaired memory, anxiety, restlessness, insomnia, urinary retention, blurred vision, and rash
Angle closure glaucoma occurs very rarely
Potential to impair mental alertness or physical coordination—use caution when driving or operating machinery until e ects on the individual are known

Pharmacokinetics

Bioavailability

Readily absorbed following oral intake

Distribution

In animals, detected in all organs (not known in humans)
Unknown if in breast milk

Metabolism

Almost completely metabolized to at least eight metabolites
Not fully determined

Elimination

Eliminated principally in the urine as metabolites
As unchanged drug (in small amounts)

Half-life

Approximately 14 hours

Interactions

Many drugs have anti-muscarinic e ects; concomitant use of two or more such drugs can increase S/Es such as dry mouth, urinary retention, and constipation; concomitant use can also lead to confusion in the elderly
Interactions are possible with TCAs, antihistamines, clozapine, codeine, domperidone, haloperidol, levodopa, MAOIs, memantine, metoclopramide, nefopam, nitrates, parasympathicomimetics, and phenothiazines
Increased sedative e ects with alcohol

Special circumstances

In the elderly: reduce dose (at lower end of range recommended)
Caution in pregnancy and breastfeeding (may cross the placenta)
Caution in renal and hepatic impairment
May a ect driving ability
Safety and e cacy not established in those under 12 years of age

Additional information

Orphenadrine is anti-muscarinic and can theoretically exacerbate epilepsy and trigger seizures. The patient needs to be warned that their antiepileptics may necessitate an increase in dose if that is the case
Avoid abrupt withdrawal

Cost

150 mL bottle (50 mg/5 mL): £42.45 (£1.42 per 50 mg)
Per month: £127–255, depending on the dose

Further reading

1. Joint Formulary Committee. British National Formulary. 2020. London: BMJ Group and Pharmaceutical Press. https://www.bnf.org
2. ASHP. Drugs.com. 2020. https://www.drugs.com/monograph/orphenadrine-citrate.html

13.16 Vitamin D

Introduction

Vitamin D is a fat-soluble vitamin, produced endogenously and obtained through food (either naturally or with forti cation) and through supplements
It controls the amount of calcium and phosphate in our body, which are needed for healthy bones, muscles, and the immune system
Vitamin D de ciency is a worldwide epidemic and approximately 1 billion people are vitamin D-de cient
In the UK, 1 in 5 people have low vitamin D
All estimated average requirements (EARs) or recommended daily allowances (RDAs) assume that there is minimal or no sun exposure
Serum concentration of Vitamin D (see table 13.16.1)

Table 13.16.1 Serum concentration of vitamin D

Vitamin D	**Plasma level (nmol/L)**
De ciency	<50
Insu cient	51–74
Normal (varies)	**75–250**
Potentially harmful	>250

Class of drugs

Vitamin D is a secosteroid, synthesized in the skin with energy from ultraviolet B light
It is hydroxylated into 25(OH)D (pro-form) and then into 1,25$(OH)_2$D (active form)

Causes of de ciency

Low sun exposure
Inadequate dietary intake
Use of creams with ultraviolet (UV) lter (protection >8)
Hyperpigmented skin
Malabsorption
Increased catabolism (use of anticonvulsants, ATT, antiretrovirals)
De cient 25-hydroxylation/1 hydroxylation

What happens with vitamin D de ciency

Rickets in infants and osteomalacia in adults
Impairs proximal muscle function and predisposes to falls in those who are vulnerable
Long-standing de ciency is a risk factor for osteoporosis
Insu ciency increases the rate of cardio-metabolic disorders, leading to an increased risk of IHD and stroke

Dose

Supplementtaion of vitamin D can be either to prevent or to treat de ciency
Vitamin D is available as D3 (colecalciferol) and D2 (calciferol)
Both D3 and D2 are equally active in humans

Loading dose

Colecalciferol D3: aim for cumulative dose of 300 000 units (usually 50 000 units/week)
Calciferol D2: between 40 000 units and 100 000 units per day (based on pathology)

Maintenance

For prevention—usually 400 units daily; for treatment of de ciency—800 units daily

Mechanism of action

Vitamin D is a potent inducer of antimicrobial peptide on immune cells.
It reduces the release of pro-in ammatory cytokines, suppresses T cell response, and inhibits the synthesis of Prostaglandin E2
Antiproliferative e ects on several types of cancer cells

Monitoring

Ca^{2+} concentration should be checked in patients receiving vitamin D at least once weekly initially

Contraindications

Hypercalcaemia, metastatic calci cation

Adverse e ects

Abdominal pain, headache, hypercalcaemia, hypercalciuria, nausea, constipation, decreased appetite

Overdose causes anorexia, nausea, vomiting, weight loss, polyuria, and increased plasma and urinary concentrations of Ca^{2+} and phosphates

Pharmacodynamics and kinetics

Vitamin D is a fat-soluble vitamin, and its absorption depends on the gut's ability to absorb dietary fat, particularly from the duodenum

Once in circulation, it binds to vitamin D-binding protein for transport and is stored in adipose tissue

After hydroxylation, it exerts its physiological action by binding to intracellular vitamin D receptor and promotes intestinal Ca^{2+} and phosphate absorption, renal tubular Ca^{2+} reabsorption, and Ca^{2+} mobilization from bones

Vitamin D is excreted mainly through bile

Special circumstances

Therapeutic doses in pregnancy unlikely harmful

In breastfeeding, high doses can cause hypercalcaemia in infants

Monitor Ca2+ levels in renal impairment

Additional information

Insu cient vitamin D levels increases pain in bromyalgia and other chronic MSK pain conditions

Low vitamin D levels are linked to increased statin- related myalgias

In patients with cancer pain, low levels of vitamin D can be associated with high opioid requirement

Low 25(OH)D levels are present in patients su ering from chronic pain, but a Cochrane review in 2015 established that supplementing chronic pain patients with vitamin D was safe, but not consistently e cacious over placebo, hence does not support vitamin D treatment as an independent treatment for chronic pain conditions (e.g. bromyalgia, non- speci c MSK pain)

Although obesity and overweight are associated with low circulating 25(OH)D levels, there is inconclusive evidence regarding its e ect on bone health

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CHAPTER 14

Clinical Pharmacology

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14.1 Analgesic ladders

In 1986, the World Health Organization (WHO) published a document entitled *Cancer Pain Relief*, which set out the principles of use of analgesics in cancer pain management, based on the use of a 'three-step analgesic ladder' (see Fig. 14.1.1). An updated version was published in 1996

The guidelines arose from evidence of poor management of cancer pain in both developing and developed countries

One of the reasons for this situation was the reluctance of health professionals to use 'strong' opioids because of misplaced fears of addiction and tolerance amongst patients, and of illegal use amongst the wider community

This legitimized and increased the prescribing of 'strong' opioids amongst patients with moderate to severe cancer pain, but also extended its use for non-cancer pain

The WHO analgesic ladder has a role in management of patients with acute pain, but a limited role in CNCP

This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 70–90% e ective for cancer, but this has led to opioid overprescribing and an opioid epidemic in non-cancer pain

In the case of cancer pain in children, the WHO recommends a two-step ladder

Adapted analgesic ladder for acute, chronic non-cancer, and cancer pain (see Fig. 14.1.2)

Principles

'By the mouth' (wherever possible)—a di erent route of administration should be considered if the oral route is not suitable

'By the clock'—patients should be given regular analgesia such that the next dose is delivered before the previous one wears o plus rescue doses at 50–100% of the regular dose

'By the ladder'—if pain occurs, there should be prompt oral administration of drugs in the following order: non-opioids (aspirin and paracetamol); then, as necessary, mild opioids

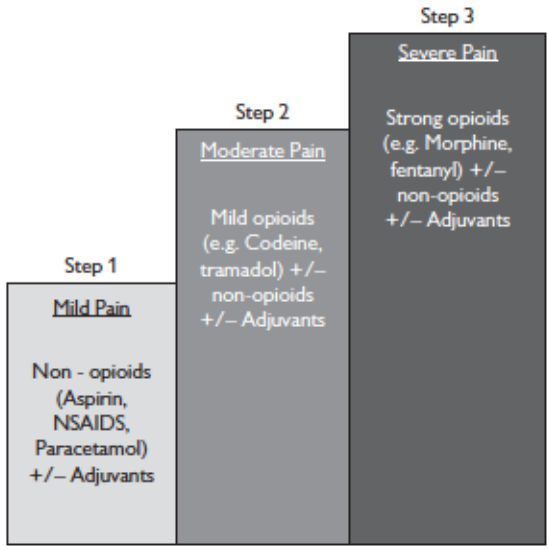


Figure 14.1.1 The WHO analgesic ladder—a three-step approach for cancer and acute pain
Reproduced with permission from Tameem, A. (2016). Analgesic ladders. In Plunkett, E., Johnson, E., Pierson, A., (Eds). *Returning to Work in Anaesthesia: Back on the circuit.* Cambridge, United Kingdom: Cambridge University Press

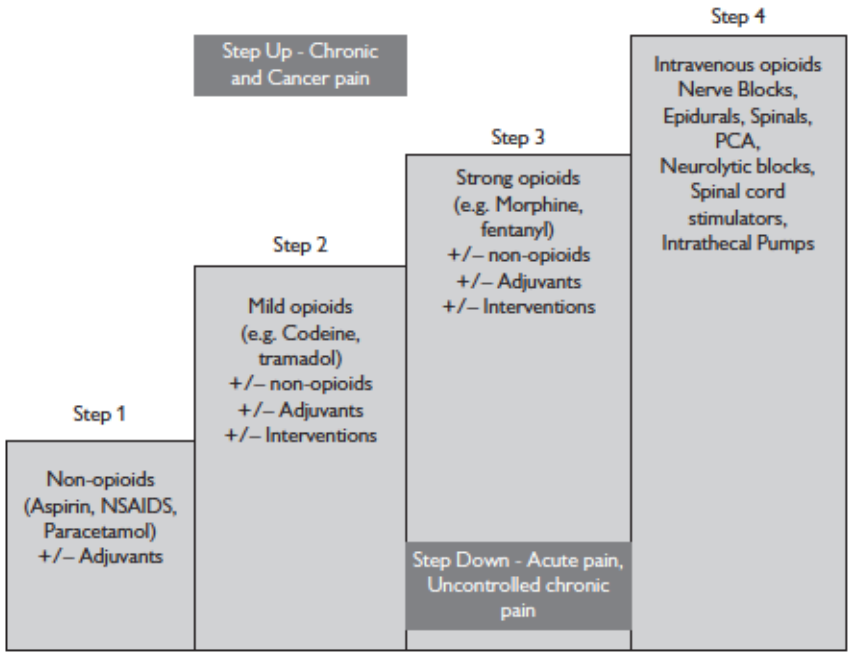


Figure 14.1.2 Adapted analgesic ladder for acute, chronic non-cancer, and cancer pain
Reproduced with permission from Tameem, A. (2016). Analgesic ladders. In Plunkett, E., Johnson, E., Pierson, A., (Eds). *Returning to Work in Anaesthesia: Back on the circuit.* Cambridge, United Kingdom: Cambridge University Press

(codeine); then strong opioids, such as morphine, until the patient is free of pain. The patient should be treated with drugs on the step that corresponds to their pain. For example, if they score pain as severe, they should be treated with drugs from step 3 (strong opioids)

'By the individual'—there are no standard doses for opioids; the right dose is the one that relieves the individual's pain. Other analgesics have a standard maximum dose, whereas opioids are titrated to achieve adequate analgesia with minimal S/Es

'Attention to detail'—individualized care involving the patient, family, and carers is vital to provide adequate analgesia

Medications

Simple analgesics: paracetamol, NSAIDs, e.g. ibuprofen, naproxen, diclofenac, COX-2 inhibitors

Weak opioids: codeine, dihydrocodeine

Strong opioids: tramadol, morphine, oxycodone, fentanyl, methadone

Adjuvants: used to enhance pain relief or treat speci c types of pain, to treat adverse e ects of analgesics, and to treat concomitant psychological disturbances, including insomnia, anxiety, and depression:

- Antidepressants: TCAs, SSRIs, and selective noradrenaline reuptake inhibitors
- Anticonvulsants: gabapentinoids, carbamazepine, oxcarbazepine, sodium valproate, lamotrigine, phenytoin
- NMDA receptor antagonists: ketamine
- -2 agonists: clonidine, dexmedetomidine
- Anxiolytics: BZDs (diazepam), hydroxyzine
- Others: steroids, baclofen, cannabinoids, lidocaine 5% patch, topical capsaicin, LAs (IV lidocaine, mexiletine)
- Antiemetics (chlorpromazine, prochlorperazine) and laxatives

The WHO analgesic ladder, despite its limitations in non-cancer pain, does provide a good framework to manage pain

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14.2 Pre-emptive and preventative analgesia in acute pain

Pre-emptive analgesia

De nition

Administration of preoperative treatment is more e ective than the identical treatment administered after surgical incision or during surgery. The key point is the timing of administration of the analgesic treatment before the onset of the noxious stimuli or skin incision during surgery

Note: an analgesic treatment given pre-emptively can also be preventative

History

Crile in 1913 suggested that pain after surgery might be ampli ed by noxious stimuli following surgical incision. The use of a multimodal analgesia, including regional LA blocks, was thought to potentially reduce this

Wall in 1988 described 'pre-emptive pre-operative analgesia'

Woolf in 1983 and 1991 described evidence of a central component of post-injury pain hypersensitivity in experimental studies and went on to suggest that changes in timing of analgesia could a ect post-operative pain control

Kissin in 1994 and Katz in 2002 found that individual clinical studies have reported con icting outcomes when comparing 'pre-incisional' with 'post-incisional' interventions. In part, this may relate to variability in de nitions, de ciencies in clinical trial design, and di erences in the outcomes available to laboratory and clinical investigators

E cacy

There are many techniques described, with con icting reports on their e cacy. The evidence is strongest for epidural neural blockade; for example, one study has shown that following thoracotomy, pre-emptive thoracic epidural analgesia reduces the severity of acute pain on coughing for up to 48 hours

Mechanism of action

Reduced central sensitization associated with a nociceptive stimulus. By administering the analgesic agent prior to an acute nociceptive stimulus, subsequent DH changes associated with central sensitization and hypersensitivity are reduced, compared with administration of the analgesic before the surgical insult has occurred and the pain is established

The development of chronic pain may be reduced through this alteration in sensory processing

Preventative analgesia

De nition

Preventative analgesia is **persistence** of an analgesic e ect beyond the expected duration of action of the agents or interventions

Administration of a preventative analgesic agent leads to a reduction in post-operative pain and/or analgesic consumption, when compared to another treatment, placebo treatment, or no treatment. This therapeutic e ect is observed at a point in time beyond the expected duration of action of the intervention (e.g. 5.5 t1/2 of the drug)

The agent or technique is used preoperatively, intraoperatively, or post-operatively

History

Kissin in 1994 suggested the term 'preventative' analgesia to be more clinically relevant than 'pre-emptive' analgesia

Dahl in 2004 described the importance of continuing the analgesic agent into the post-operative recovery period to allow ongoing reduction in central sensitization

Katz in 2011 described the focus of preventative analgesia or interventions not being on the timing of their administration, but on their overall ability to impact on reducing the nociceptive barrage associated with noxious preoperative, intraoperative, and post-operative stimuli

E cacy

There is evidence to support that ketamine is an e ective preventative analgesic

LAs (either systemic or perineural) are preventative analgesics, reducing acute pain in the perioperative period. Intraoperative neuraxial block and systemic LAs may be e ective in major abdominal procedures

The evidence for whether NSAIDs and gabapentinoids are preventative analgesics is less convincing

Mechanism of action

Persistent analgesic e ect is achieved by minimizing sensitization induced by noxious perioperative stimuli, leading to reduction of central sensitization and 'wind-up'. This action occurs in di erent ways, depending on the drug or technique involved, and may reduce the risk of developing chronic pain

Peripheral sensitization is reduced by a decrease in the local in ammatory response caused by tissue damage. For example, NSAIDs reduce the production of PGs that lead to transduction and increased conduction of nociceptive impulses to nociceptive selective and wide dynamic range neurons in the DH, resulting in altered responsiveness of these neurons

A reduction in the barrage of pain signals from nociceptors to neurons in the DH leads to less hyperresponsiveness and hence decreased central sensitization

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14.3 Management of patients with a substance use disorder

Introduction

Management of patients with acute and/or chronic pain on prescription drugs can be challenging

Opioid prescription drug abuse is the most common. There has been large-scale prescription of opioids for all types of pain since the early 1990s, owing to publications asserting that the risk of addiction and abuse is low in patients receiving opioids for chronic pain

The prevalence of prescription opioid abuse ranges from 1% to 40% in patients with CNCP due to di culties in diagnosing abuse in this patient population

While patients did bene t from increased access to opioids, there has been an alarming increase in opioid misuse, abuse, and opioid-related mortality and morbidity

Other prescription drugs that are abused include BZDs, gabapentinoids, barbiturates, and cannabis

De nitions

For important de nitions on substance abuse and addictive behaviours, see 4.5 Tolerance, dependence, addiction, and pseudoaddiction, p. 87

Withdrawal

Opioid withdrawal occurs when the opioid dose is stopped or rapidly tapered, or when an opioid antagonist is given

There may be psychological e ects, which include craving and agitation, and physical symptoms such as diarrhoea, palpitations, or tachycardia

Diversion

Diversion is the transfer of prescribed opioids for unlawful use

Prescription opioids may be passed on or sold to persons other than the patient, for therapeutic or recreational use

Doctors have a legal and ethical responsibility to uphold the law and to protect society from drug misuse

Opioids must be responsibly prescribed, and health care professionals must be vigilant for, and guard against, misuse, while also ensuring that patients have the required medication available

Assessment of patients

Should be done in a **multidisciplinary pain clinic** by applying the biopsychosocial model, using pharmacotherapy, physical therapies, cognitive behavioural/psychological therapies, and exercise

A single practitioner/pain clinic/GP surgery and a single pharmacy should be responsible for opioid prescriptions and dispensing, respectively

A thorough history (especially of substance abuse and medication list with doses) and physical examination are of utmost importance

Signs of medication abuse:

- Include signs of intoxication or withdrawal, requesting for early reissuing of opioids, approaching a second physician and/or pharmacy, stealing or buying opioids from other patients or on the Internet, exaggerated pain behaviour, ine cacy of alternative treatments, needle marks, being assertive, aggressive, or emotionally labile, a vague or crisp history of symptoms, and refusing tests such as urine toxicology

Predictors of prescription drug abuse include:

- Social factors: family history of substance misuse, substance misusers in social network, current victim of abuse, occupational risk
- Psychological factors: abuse, trauma, anxiety disorders, PDs, current or previous substance abuse

Psychological screening:

- Psychological disorders are common in patients with substance abuse. A psychologist should assess and manage these issues. Tools such as the HADS should be used
- Use tools to assist in identifying at-risk patients: tools include CAGE-AID (adapted to include drugs), Prescription Drug Use Questionnaire (PDUQ), Screening Instrument for Substance Abuse Potential (SISAP), the Screener and Opioid Assessment for Patients with Pain (SOAPP), and the Opioid Risk Tool (ORT)

Pill counts: evaluate the use of prescribed opioids, which can also be part of an adherence monitoring programme to reduce opioid abuse. Attempt should be made to di erentiate between addiction and pseudoaddiction

Assess the **four As** (analgesia, activities of daily living, adverse e ects, and aberrant drug-related behaviours)

Investigations:

Urine toxicology, -glutamyl transpeptidase, hepatitis B and C antigen titres, and HIV tests should be considered

Urine toxicology: immunoassay urine screens are often used as the rst line of analysis and detect the presence of prescription and illicit drugs. Gas chromatography/mass spectrometry urine screens quantify the extent of illicit and prescription drug use

Patient strati cation

Low risk (can be managed in primary care): patients have no history of substance abuse or positive predictors. They admit to taking extra doses and can be managed by education and close follow-ups

Medium risk (need specialist support): patients may have a history of substance abuse and some positive predictors. Specialist advice or referral is needed for these patients

High risk (need specialist management): patients have a history of active substance abuse and/or an untreated psychiatric disorder. These patients need an urgent referral to addiction specialist services

Management

High and complex patient needs: these patients have greater needs than opioid-naïve patients, making multidisciplinary team input necessary. They may also need referral to addiction services and social services

Explanation of management plan: clear **goals** of treatment should be established and frequent assessment of progress towards these goals should be done. Patients should be explained about the **adverse e ects of opioids**, the amount of opioid analgesia they can expect, that opioids are not the answer to all the pain, and that non-opioid drugs and non-pharmacological interventions will be bene cial for them. All discussions must be **clearly documented** and communicated to other members of the health care team

Choice and route of opioid: the **same opioid** should be used, as this will make dose calculation easier and will avoid S/Es of a new agent. The oral route is preferred as this allows easier dose titration. **Long-acting preparations are of lower abuse potential**

Short-acting preparations and lipid-soluble opioids result in a rapid increase in opioid blood and CNS concentrations, which can give a 'high' feeling

Lipid-soluble opioids (fentanyl and pethidine) and short-acting preparations of other opioids (morphine, oxycodone, hydromorphone) are to be avoided

Transdermal preparations can be useful in such patients as they do not cause a rapid rise in plasma concentrations

The entire amount of opioid should preferably be given as long-acting preparations

In select cases, breakthrough analgesia may be provided with short-acting opioids, but these patients need to be carefully monitored

These patients are tolerant of the usual doses of opioids, so they need higher doses, along with the maintenance dose of their usual opioid

Contracts/opioid therapy agreement: these are agreements that clarify the roles, responsibilities, and limitations between the prescriber and the patient. It is advisable to use contracts when prescribing long-term opioids. If the conditions of the contract are not met, opioid therapy may be withdrawn. A **trilateral agreement** between the pain physician, the GP, and the patient is made if the GP will be prescribing the opioids

Close monitoring (including monthly urine toxicology and compliance checking) and cognitive behavioural counselling: these have shown to improve opioid prescription compliance in high-risk patients

Patients with psychopathology and psychiatric disorders need input from a psychologist and/or psychiatrist, and adequate **social support** through social services is important. This includes nancial support, housing, and help if in an abusive relationship

Non-opioid pharmacotherapy: NSAIDs, paracetamol, antidepressants (TCAs, selective noradrenaline reuptake inhibitors), and gabapentinoids (gabapentin and pregabalin) can be added as part of a multimodal analgesic regimen

Pain interventions: where indicated, interventions such as facet joint blocks, ESIs, and TPIs, amongst others, should be o ered

Acute pain management in patients abusing prescription opioids

These patients are opioid-tolerant and consequently require higher doses than opioid-naïve patients

There is no speci c dose at which patients are considered opioid-tolerant; however, the FDA has issued guidelines for de ning opioid-tolerant patients

Opioid-tolerant patient: one taking 60 mg of oral morphine per day or an equianalgesic dose of another opioid for 1 week or longer

Di culties faced in the assessment of pain in opioid-dependent patients

Standard methods of assessment of pain and response to therapy are less accurate in these patients, and distrust between these patients and physicians can act as a barrier in the assessment and provision of optimal pain treatment

Patients fear that their analgesic medication will be withheld, leading to anxiety, fear of withdrawal, and drug-seeking behaviour

Fear of respiratory S/Es at unusually high doses that these patients require leads to health care providers underprescribing opioids

It may be di cult to obtain an accurate history of the dose of opioids being taken

Patients often report higher pain scores, may fabricate pain behaviour, and have increased opioid requirements

Patients may be abusing other drugs and may divert prescribed opioids

Assessment of pain in opioid-dependent patients

Discuss clearly the pain management plan and build an environment of trust with the patient

A good rapport will help in accurately ascertaining which drugs the patient is taking and understanding expectations

The dose of opioids and other drugs should be obtained as accurately as possible. This will help in calculating the total dose of drug to be given per day

Early involvement of the **inpatient pain team (IPT)** is required. In patients going for surgery, preoperative engagement with the IPT should be considered

It is important to get information about the patient's drug history from the primary care physician and addiction team (if known to them)

These patients have a high prevalence of psychiatric comorbidities, such as anxiety and depression, which need to be addressed

Along with the usual pain assessment tools, such as VAS and NRS, other measures, such as ability to breathe deeply, cough, ambulate, and engage with physiotherapy, signs of withdrawal, opioid S/Es, and mood, should be assessed

Urine screening could be considered to help formulate a better management plan

Assessment of psychiatric comorbidities, medical comorbidities, and social factors

Do not attempt counselling about substance abuse and/or detoxi cation in the acute pain stage

Prescribing opioids and other analgesics during an episode of acute pain

Continue baseline opioid: determine the baseline opioid requirement per day. This amount should be given to prevent withdrawal

Route: the patient's normal route (oral or transdermal) should be continued, if possible. In general, the oral route is preferred. Long-acting opioids should be given if the oral route is used

If the patient is unable to take opioids orally, a continuous infusion, PCA, or intermittent boluses can be given. PCA will usually need to be at a higher dose than usual, including increased bolus dose and addition of a background infusion

Choice of opioid: try to use the same opioid the patient was taking, as this will make it easier to calculate the total drug required and prevent S/Es from a new agent

Additional or breakthrough analgesia: along with the background dose of opioid, additional opioids can be provided by PCA or intermittent boluses of opioids. NSAIDs, paracetamol, ketamine, GCs (dexamethasone), magnesium, gabapentinoids (gabapentin and pregabalin), and -2 agonists (clonidine and dexmedetomidine) can be added as part of the multimodal analgesic regimen. Regional analgesia and central neuraxial analgesia should be used where appropriate

Role of adjuvants: drugs such as ketamine (low dose), GCs, magnesium, gabapentinoids, and -2 agonists improve analgesia and can also be used to manage OIH and opioid tolerance

Patients on opioid substitution therapy (OST): certain patients may be on OST such as methadone or buprenorphine. This needs to be continued and other opioids and analgesics are added to provide optimal analgesia

Discharge analgesia: these patients need to be discharged on opioid medication and should be referred to the pain clinic and/or addiction clinic for continued management and support

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14.4 Serotonin syndrome

Introduction

Impaired mental state, increased muscle activity, and autonomic instability secondary to excessive serotonin (5-HT) activity in the brainstem and spinal cord

Seen in SSRI overdose, particularly in combination with other antidepressant drugs such as SNRIs, MAOIs, and TCAs

Also associated with use of tramadol, tapentadol, pethidine, fentanyl, metoclopramide, ondansetron, amphetamines, and cocaine—particularly if these are taken with SSRIs and SNRIs

Diagnosis

Diagnosis is made clinically (based on presentation and drug history)

Di erential diagnosis: neuroleptic malignant syndrome, malignant hyperthermia, anticholinergic toxicity, heat stroke, meningitis

Clinical presentation

Incidence: rare (approximately 15% of SSRI overdoses develop serotonin syndrome)

Clinical triad of abnormalities

Cognitive e ects: confusion, headache, agitation, hypomania, hallucinations, coma

Autonomic e ects: shivering, sweating, hyperthermia (can be >40°C), vasoconstriction, tachycardia, nausea, diarrhoea

Somatic e ects: myoclonus, hyperre exia, clonus, tremor

Complications

Disseminated intravascular coagulation, cardiac failure, renal failure, rhabdomyolysis

Treatment

Cessation of precipitant drugs

Activated charcoal has a role if given within 1 hour of ingestion

5-HT antagonists: cyproheptadine rst line, methysergide. Consider olanzapine for severe cases

Supportive care, including control of autonomic instability:

- BZDs to control myoclonus and reduce hyperthermia
- Active cooling if hyperthermia severe
- Muscle relaxation with intubation and ventilation for severe cases—avoid suxamethonium due to increased K^+ levels
- Maintain high urine output to limit renal dysfunction

Prognosis

Usually resolves within 24 hours; death has been reported rarely. Muscle pain and weakness can persist for months

Additional information

Serotonin syndrome presents with hyperkinesia and clonus

In contrast to bradykinesia and extrapyramidal 'lead pipe' rigidity that is seen in neuroleptic malignant syndrome

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14.5 Placebo and nocebo

Placebo

A *placebo* is de ned by Shapiro and Morris as 'any therapy or component of therapy used for its nonspeci c, psychological or psychophysiological e ect or that is used for its presumed speci c e ect, but is without speci c activity for the condition being treated'

The *placebo e ect* describes 'the positive response some patients/participants experience after receiving a placebo. When present, this response has a perceptible and measurable bene cial e ect that may be subjective (e.g. pain reduction) or objective (e.g. improved blood pressure). These e ects are believed to be related to intrinsic factors (e.g. personal expectations or learnt responses) and/or extrinsic (e.g. provider, environment, technology, and contextual) factors'

Placebo e ects have an important role in three areas: (1) as controls in experimental studies to determine speci c e ects and enable blinding; (2) in placebo research; and (3) as a tool in clinical practice

Nocebo

Nocebo derives from the word *nocere*, meaning '*I shall harm*'

The *nocebo e ect* is 'the negative response some patients/participants experience after receiving a placebo. These e ects range from minor discomforts (e.g. headache, nausea) to life-threatening complications'

The underlying mechanisms are both psychological (conditioning, negative expectations) and neurobiological (via cholecystokinin, dopamine, and endogenous opioids)

Nocebo e ects can in uence clinical outcomes and treatment adherence. Gaining a deeper understanding of the nocebo e ect may help in identifying factors that lead to maladaptive responses. For instance, clinicians communicate via both verbal and non-verbal techniques, some of which may unintentionally impart negative suggestions that may trigger a nocebo response. Therefore, carefully balanced clinician–patient communication (positive framing, contextualized informed consent) and exploring patients' treatment beliefs may mitigate the nocebo e ects

History

In medieval times, mourners were hired to attend funerals, but because their emotions were considered insincere, they were called '*placebos*', from the Latin for '*I will please*'

Henry Beecher (an eminent American anaesthesiologist and medical ethicist), in 1955, published a paper entitled '*The powerful placebo*', in which he wrote: '*placebos have a high*

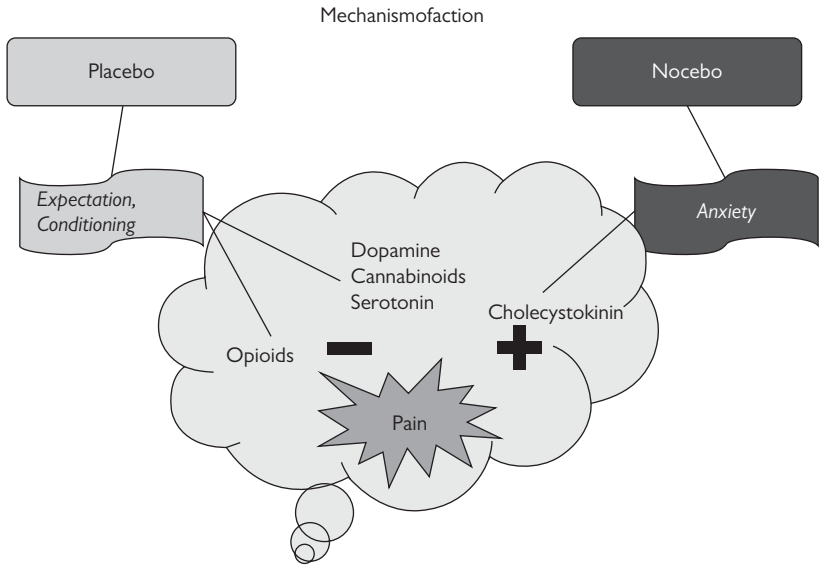


Figure 14.5.1 Mechanisms of placebo analgesia

degree of therapeutic e ectiveness in treating subjective responses.' This paper, in which he noted that placebos are e ective 30% of the time, had a profound e ect on clinical research

Mechanisms of placebo analgesia

(See Fig. 14.5.1.)

Psychological mechanisms

Psychological traits such as empathy, dispositional optimism, hypnotic suggestibility, neuroticism, altruism, and the locus of ego-reliance have been linked to the e cacy of placebo analgesia

Brain mechanisms

Placebo analgesic e ects have been shown to produce activity changes and enhanced functional coupling in the dorsolateral prefrontal cortex (DLPFC), the rostral anterior cingulate cortex (rACC), and the subcortical regions, including the hypothalamus, amygdala, and PAG

The DLPFC initiates the placebo analgesic response. The rACC is connected to the PAG and correlates with modulation of placebo analgesia

fMRI shows that the activity at the level of the spinal cord is modulated by placebo analgesia

Placebo analgesia may be due to the endogenous release of neuropeptides such as opioids, cholecystokinins, dopamine, serotonin, and cannabinoids, an e ect which may be reversed by naloxone

Genetics and the placebo response

The study of genomic e ects on the placebo response has been termed the 'placebome'

Genetic polymorphism in the expressing of the dopaminergic and serotonergic mechanisms which are responsible for placebo analgesia may mean that placebo responses vary by genotype

In general, the placebo arm is considered to be an adequate control for outcomes in the active treatment arm of RCTs. However, if the placebo response does indeed vary by genotype, we might expect challenges with confounding, potential gene–drug–placebo e ect modi cation, and disease-speci c e ects

Recent advances

Open-label placebo (OLP) breaks from the received wisdom that clinical administration of a placebo requires deception (or double-blind conditions) to be e ective—several studies have directly tested the e ect of an OLP prescription, and all indicated that patients reported bene ts after taking pills presented honestly as placebos

It has been postulated that 'engendering hope when participants feel hopeless about their condition can be therapeutic'

Another possible explanation is the Hawthorne (or observer) e ect: a person who is aware of being studied/observed often feels better, even if nothing has actually changed—this is also why patients say they feel better when their attending doctor or nurse is attentive and has good bedside manners

Conclusion

As our understanding of the placebo evolves, it is worth bearing in mind the advice by the American Institute of Medicine: '*placebo (can) conceivably be a form of treatment of pain, especially in light of the shortcoming of other modalities or bene ts they bring in their right*'

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SECTION 4

PAIN INTERVENTIONS

CHAPTER 15

Overview of Interventions

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15.1 Overview of pain interventions

Introduction

A pain block is an invasive intervention intended to reduce a patient's pain levels and improve their mobility, activity levels, sleep, and QoL

Interventional pain management should be part of a multidisciplinary management plan

Factors a ecting patient selection and speci c intervention o ered

Clinical history:

- The nature, distribution, and frequency of pain
- Previous surgery or interventions for pain management
- The impact of pain on the patient's daily routine, working life, and QoL
- Assessment of the patient's physical, psychological, and environmental factors

Pain-orientated clinical examination:

- MSK ± neurological examination
- Areas of tenderness
- Positive/negative features of neuropathic pain

Investigations (these may vary as per procedures):

- Blood tests (haematology, biochemistry, coagulation, glycaemic pro le)
- X-rays, CT scans, MRI,US, bone scans
- Nerve conduction studies (NCS)

Exclude serious pathology (e.g. infection, fracture, cauda equina syndrome, tumour)

Identify the underlying cause of the pain

Advanced interventional procedures should be done in a multidisciplinary pain management unit and after more conservative therapies have been tried

Resources, adequately trained sta , evidence, and cost of the procedure should be taken into consideration

Patient factors a ecting suitability for procedure

Pain symptoms, signs and investigations correlate with the planned procedure

Patients and clinicians must have realistic expectations of the outcome of the procedure

Patients understand that they need to engage actively and take responsibility for their pain management strategy

Consideration of factors that may be associated with poorer outcomes in interventional pain medicine (e.g. catastrophization, uncontrolled mental health disorders, low self-e cacy, unrealistic expectations, active substance use disorder, use of passive pain management strategies, secondary gain, fear avoidance behaviours, inappropriate use of opioids or other medications, ongoing compensation)

Absolute and relative contraindications:

- Medically unwell—poorly controlled cardiovascular, respiratory, renal, and other medical conditions
- Coagulopathy and/or intake of antiplatelet or anticoagulant drugs
- Active infections and avoid if high risk of developing infections (e.g. diabetes, immunosuppression)
- Pregnancy (especially procedures involving ionizing radiation)

Consent

Mutual decision process between the patient and the clinician(s)—this should be a staged process (e.g. discussion in clinic, use of Internet resources or lea ets, nal consent signed or countersigned on the day of the procedure)

Communication must be clear, and the patient must be able to understand its nature, possible risks, and complications (e.g. failure, discomfort, bruising, haematoma, infection, are-up of pain symptoms, allergic reaction, temporary/permanent neurological symptoms, damage to surrounding structures and other complications speci c for the procedure being performed)

Discussion of realistic outcomes (e.g. possible failure of the procedure to relieve pain, reduction of pain severity, improvement in function, reduction of use of analgesia, reduction of S/Es from medications)

Explaining the evidence of the intervention

Discussion of potential alternative treatments and impact of not having the speci c intervention

Maximizing the patient's ability to make decisions themselves and respecting those decisions

Answering the patient's questions and respecting their autonomy

The clinician is responsible for ensuring the patient has capacity to consent for a procedure

The team involved must be competent to perform the procedure

Patients can have access to a second opinion if required

Performance of the procedure

Use of a checklist is recommended during procedures (see Fig. 15.1.1)

Pre-procedure instructions to the patient

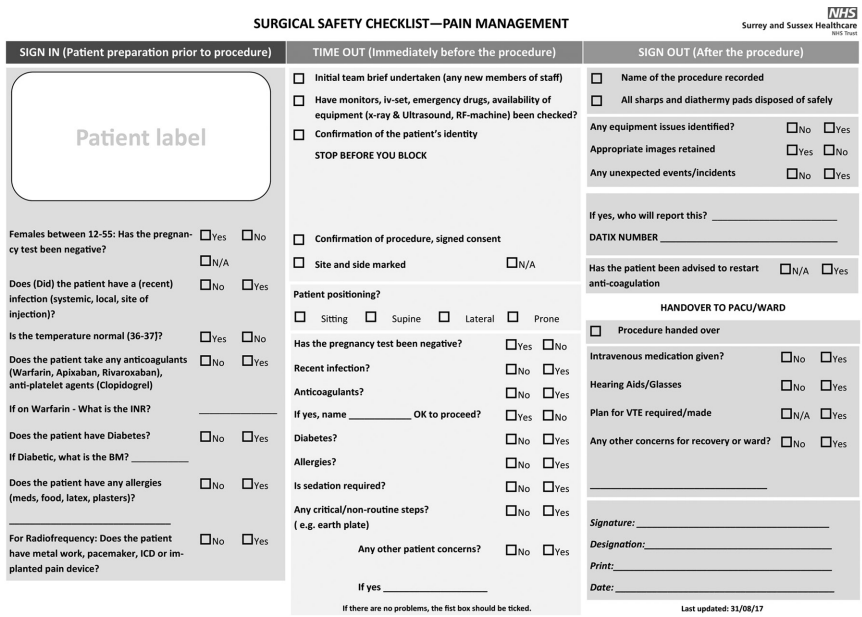
Adjustment of medications (e.g. anticoagulants, hypoglycaemics, etc.)

Fasting instructions may or may not be needed

Information about the planned procedure(s) (e.g. local or pain faculty lea ets, Internet resources)

Further management after the procedure (e.g. physiotherapy, psychology, occupational therapy (OT), biomedical treatments/resources in primary ± secondary care)

Ensuring adequate support is available for attending the procedure appointment and discharge afterwards (e.g. hospital transport, relative, partner, or friend picking the patient up and staying with them overnight)



SURGICAL SAFETY CHECKLIST—PAIN MANAGEMENT

NHS Surrey and Sussex Healthcare NHS Trust

SIGN IN (Patient preparation prior to procedure)

Patient label

Females between 12-55: Has the pregnancy test been negative? ☐Yes ☐No ☐N/A

Does (Did) the patient have a (recent) infection (systemic, local, site of injection)? ☐No ☐Yes

Is the temperature normal (36-37)? ☐Yes ☐No

Does the patient take any anticoagulants (Warfarin, Apixaban, Rivaroxaban), anti-platelet agents (Clopidogrel) ☐No ☐Yes

If on Warfarin - What is the INR? _____

Does the patient have Diabetes? ☐No ☐Yes

If Diabetic, what is the BM? _____

Does the patient have any allergies (meds, food, latex, plasters)? ☐No ☐Yes

_____

For Radiofrequency: Does the patient have metal work, pacemaker, ICD or implanted pain device? ☐No ☐Yes

TIME OUT (Immediately before the procedure)

☐ Initial team brief undertaken (any new members of staff)

☐ Have monitors, iv-set, emergency drugs, availability of equipment (x-ray & Ultrasound, RF-machine) been checked?

☐ Confirmation of the patient's identity

STOP BEFORE YOU BLOCK

☐ Confirmation of procedure, signed consent

☐ Site and side marked ☐N/A

Patient positioning?

☐ Sitting ☐ Supine ☐ Lateral ☐ Prone

Has the pregnancy test been negative? ☐Yes ☐No

Recent infection? ☐No ☐Yes

Anticoagulants? ☐No ☐Yes

If yes, name _____ OK to proceed? ☐Yes ☐No

Diabetes? ☐No ☐Yes

Allergies? ☐No ☐Yes

Is sedation required? ☐No ☐Yes

Any critical/non-routine steps? (e.g. earth plate) ☐No ☐Yes

Any other patient concerns? ☐No ☐Yes

If yes _____

If there are no problems, the fist box should be ticked.

SIGN OUT (After the procedure)

☐ Name of the procedure recorded

☐ All sharps and diathermy pads disposed of safely

Any equipment issues identified? ☐No ☐Yes

Appropriate images retained ☐Yes ☐No

Any unexpected events/incidents ☐No ☐Yes

If yes, who will report this? _____

DATIX NUMBER _____

Has the patient been advised to restart anti-coagulation ☐N/A ☐Yes

HANDOVER TO PACU/WARD

☐ Procedure handed over

Intravenous medication given? ☐No ☐Yes

Hearing Aids/Glasses ☐No ☐Yes

Plan for VTE required/made ☐N/A ☐Yes

Any other concerns for recovery or ward? ☐No ☐Yes

_____

Signature: _____

Designation: _____

Print: _____

Date: _____

Last updated: 31/08/17

Sample checklist for interventional pain management procedures

Reproduced courtesy of Surrey and Sussex NHS Trust

Performance of procedure

Available resources and adherence to local/national guidelines to perform the treatment as per national safety standards

Infection prevention and control

Appropriate patient monitoring (ECG, BP, pulse oximetry, glycaemic levels, capnography).

If patient requires general anaesthesia to have the care of an Anaesthetic Team with the appropriate resources and monitoring as per national safety standards

Availability of required resources (cannulation equipment, IV uids, vasoactive drugs, Intralipid®), and sta must be competent in advanced resuscitation

Light sedation may be o ered, where appropriate, for pain procedures if adequate facilities and support are available. The most commonly used agents are midazolam 1–2 mg, propofol 10–20 mg boluses, fentanyl 25–100 mcg, and alfentanil 0.25–1 mg.

Generic equipment required:

- Needles: 25G and 23G 38 mm hypodermic needles for skin and SC skin in ltration and speci c needles for the procedure (e.g. spinal needles, Tuohy needles, Racz introducer needle and Racz catheter, regional block needles)
- IV cannula as required
- Imaging required for the procedure (uoroscopy, CT, USS, MRI, or other).
- Contrast may be needed to determine the correct position of the needle with uoroscopy and CT
- LA:
  - Short-acting LA (e.g. lidocaine 1%) for skin/SC tissues
  - Injectate—low concentration to avoid motor block, but depends on procedure
  - Bupivacaine/levobupivacaine 0.1–0.5%, ropivacaine 0.2–1%, lidocaine 1% or other

Adjuvants can be used in an attempt to prolong the duration of some blocks, such as steroids, but the bene t of steroids is not entirely clear at the time of the publication (e.g. methylprednisolone acetate 'Depo-Medrone®', triamcinolone 'Kenalog®', or non-particulate steroids such as dexamethasone). Other adjuvants that can be used are adrenaline bicarbonate and clonidine (for further information, see Chapters 6, 12, 13.8 Clonidine, p. 244)

Clinicians should ensure that the documentation of procedures is consistent with recommendations of their National Pain Society (see Fig. 15.1.2)

Department of Pain Management
Operation Notes

Date:
First Name:
Surname:
Date of Birth:
Hospital:

Pain Consultant/Doctor:

Diagnosis:

Anaesthetist:

Procedure: **Side**: Left/Right/Bilateral
Level if applicable:

Venflon gauge: 22G / 20G / 18G / 16G Venflon site:

Sedation: yes/no Midazolam_____mg; Fentanyl_____mcg; Propofol_____mg; Other _____

Guidance: Fluoroscopy / Ultrasound / None

Position: Supine / Prone / Lateral / Sitting

Asepsis: Cap / Mask / Gown / Gloves
0.5% Chlorhexidine / 2% Chlorhexidine / Betadine
Air-dried: yes/no

Local infiltration: _____ mL of_____% lidocaine

Needle: _____G Spinal/Insulated RF/Hypodermic/Tuohy/Block needle/NR Fit

Contrast: Omnipaque 240 / 300; yes / no; _____mL
Niopam _____mL

Local anaesthetic: _____mL of_____%Bupivacaine / Lidocaine / Other_____

Steroid: _____mg of Triamcinolone / Depo-Medrone / Dexamethasone

Diluent:

Postop care and Comments:
Spray / Dressing
Monitoring:
Home when safe and mobile
Discharge / Follow-up

Sample of procedure documentation

Post-procedure instructions

- Monitoring for S/Es of the intervention in a recovery area—ensure patients have normal lower limb function and are able to pass urine prior to discharge; a member of staff should support them when mobilizing after the procedure (e.g. standing up, walking to the toilet)
- Patients must have clear instructions and contact details, should they develop S/Es after discharge (in acute cases, the emergency department of the nearest acute hospital should be attended)
- Patients should be followed up and assessed post-procedure (e.g. by telephone or clinic appointment) (see Fig. 15.1.3). Reduction in pain severity or distribution and impact on QoL should be assessed, ideally with an outcome questionnaire (e.g. NRS and timeline, Oswestry Disability Index, HADS, BPI, PCS, PSEQ, Global Impression of outcome)

Dr_____
Dept of Pain Management

Patient Details

Protocol for evaluation of effect of the test block for a diagnostic investigation

Type of injection: _____

Date: _____

Pain Evaluation

Please indicate how much of your 'normal' pain you have left at every time interval as per the chart (0% means no pain and 100% means your pain is unchanged)

Please mark with an 'X' on the chart

	0% (no pain)	100% (worst pain)
Before the block 100%	←	→
1 hour after block	←	→
2 hours after block	←	→
4 hours after block	←	→
6 hours after block	←	→
8 hours after block	←	→
12 hours after block	←	→
1 week after block	←	→
2 weeks after block	←	→

When did the pain return to your 'usual' level? Date: _____

Figure 15.1.3 Sample of post-procedure self-evaluation questionnaire

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15.2 Safety in interventional pain procedures

Introduction

One of the best-known aphorisms in medical practice is 'Primum Non Nocere'—First Do No Harm—re ecting the basic fact that complications from medical care may sometimes overshadow the diseases they were meant to alleviate in the rst place

This is especially true in the practice of interventional pain medicine where complications in treating what is otherwise a non-life-threatening condition can have catastrophic implications for the patient, as well as for the treating physician

In a closed claims study, Fitzgibbon and colleagues found 97% of closed claims in pain management malpractice suits were related to invasive procedures

There are many potential adverse e ects of these interventions, with the most feared complications being direct spinal cord or nerve injury (mostly in the setting of deep sedation), injury to critical blood supply (especially, but not limited to, spinal radicular arteries, anterior spinal artery and vertebral arteries, epidural haematomas resulting in spinal compression), infections, especially neuraxial infections, and pneumothorax

Being mindful of the risks involved in interventional pain medicine and adopting a routine that incorporates the considerations outlined below into your daily practice will undoubtedly serve to protect both you and the patient from professional and personal tragedies

General considerations

There are many factors that play a role in increasing the likelihood of complications from pain interventions

These can be broadly divided into physician- (and other sta member), equipment- (errors, technical faults), and patient-related factors

Physician-related

These include insu cient knowledge or experience of the physician, communication problems between sta members, and unawareness of institutional and expert panels' safety rules and regulations and recommendations

More mundane factors, such as workload, tiredness, and lapses in concentration, may also play a major role in reducing procedural safety

Equipment-related

There is a wide variety of technical aspects to interventional pain medicine, from the choice of speci c needles for speci c procedures (e.g. sharp versus blunt needles, straight versus curved needles) to more complex radiofrequency (RF) devices, spinal cord stimulators, and intrathecal pumps

All have their own safety pro les, maintenance requirements, and recommended pre-procedural and intra-procedural safety checks

Good knowledge of these and extreme care regarding their implementation are required from any professional conducting pain procedures

Patient-related

Poor patient selection may be a crucial factor in local complication rates

Elderly patients, complex medical comorbidities, polypharmacy, bleeding diatheses and pharmacological anticoagulation, immunosuppression, extreme obesity, diabetes, abnormal anatomy, complex physical disabilities, cognitive impairment, and previous complications or adverse reactions all signi cantly increase the risk of serious adverse e ects from any interventional approach

Practical considerations

By adhering to simple and rather common sense rules and adopting a safety-oriented working routine, it is possible to minimize the risk of severe complications and adverse events

Physician-related

Keep updated and maintain your skills (this cannot be overstated)

Never perform procedures with which you are not familiar and comfortable without expert supervision

It is imperative that you possess some sort of formal training in the procedures you are performing (e.g. completion of a recognized fellowship programme, Fellow of Interventional Pain Practice (FIPP), Certi ed Interventional Pain Sonologist (CIPS) certi cation)

Be informed of the latest recommendations/guidelines and act according to acceptable best practice, evidence, and safety guidelines of recognized professional organizations and expert opinions (e.g. do not use particulate steroid injections for transforaminal cervical injections, use blunt needles for certain procedures, etc.)

Do not perform procedures when you are sleep-deprived, shortly after international travel across >3 time zones, or if you are unwell or un t

Never perform an interventional procedure based on a single plane view—you should always verify the needle position in two planes

It is advisable to inject contrast and observe the run-o . If in doubt, take more images in di erent planes. You may also consider a test dose of lidocaine

If you are still unsure, either adjust and reassess or abort

When considering a complicated, unusual, or controversial procedure, always consult a colleague beforehand and document this in the patient's records

Be extremely careful with every procedure in the upper body, especially head and neck procedures

Sedation **signi cantly increases** the risk of serious complications and is to be avoided, if possible. Routine use of sedation for common procedures should be discouraged

This is especially true for high-risk procedures, as mentioned earlier, and targeted interventions of the peripheral nerves

Remember, a patient who talks is a patient who breathes and would also let you know if you inadvertently touch neural tissue

Monitor patients for a sufficient period after the procedure (extend the monitoring period after a difficult procedure, an unusual patient reaction, or a prior history of complications, after giving large quantities of LAs, after head and neck procedures, or in at-risk patients)

Equipment-related

Meticulously follow the maintenance and daily care instructions of your equipment. Store equipment only in conditions recommended by the manufacturer

Never use equipment with which you are not familiar without supervision

In devices with safety settings, make sure these are active

Never use medications without first double-checking the expiry dates and doses administered

Always have in hand adequate equipment to cope with a medical emergency. This is especially true for every procedure under sedation, every patient who is at risk, and every procedure in the head, neck, or thorax

Patient-related

Patient selection and tailored preparation are vital. Familiarize yourself with the risk factors for interventional procedures as outlined earlier and in the literature

Take a careful history, especially focusing on allergies, medical conditions, medications (especially anticoagulants and immunomodulators), food supplements, and previous procedures and complications. Make sure you make necessary adjustments of medications if required (e.g. steroid supplementation if steroid-dependent, changing insulin doses as required, stopping antiplatelet/anticoagulation if indicated, reducing high doses of opioids)

If necessary, clear the procedure in advance with relevant consulting physicians

Always consider whether you need to make specific adjustments for the patient's habitus (obesity or cachexia), abnormal anatomy (such as local tumour infiltration and anatomical variants), or specific limitations (e.g. inability to lie in a certain position for long periods)

Patient education—make sure the patient understands the procedure, the alternatives, possible expected physiological implications (e.g. hyperglycaemia if steroids are given, diarrhoea in coeliac plexus block), and possible adverse events and their incidence

If there is a need for translation, arrange for a translator and do not rely on poor language understanding or gesticulations

After the procedure, make sure the patient understands post-operative care instructions (glucose blood monitoring, mobility, etc.). Take extra care to ensure the patient understands when he/she should seek medical advice

Make sure to mark the body area you will be targeting and always double-check with the patient immediately prior to the procedure

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15.3 Fluoroscopy, computed tomography, and ultrasound-guided procedures

Introduction

Procedures for pain relief can be done using uoroscopy (X-ray), CT, and US guidance for improved patient safety and outcomes

Fluoroscopy

Basic principles

Use of X-ray radiation to visualize osseous structures

Use of an emitter from which X-rays emerge and an image intensi er which transmits images to a processing module

The X-ray generator is portable and C-arm-shaped, which allows for biplanar imaging of structures

Key parameters include:

- Voltage determining the strength of X-ray penetrability (e.g. 90 kV provides better penetration than 70 kV, but higher exposure to ionizing radiation)
- Current determining the quantity of radiation, and hence image density
- Magni cation determining the size of the radiation cone

Advantages of uoroscopy-guided interventions

Familiarity with clinicians

Good visualization of bony structures

Ability to visualize the injectate by visualizing radio-opaque contrast to reduce iatrogenic complications and to deliver the treatment to the correct anatomical target

Disadvantages of uoroscopy-guided interventions

Lack of visualization of soft tissues such as blood vessels, nerves, visceral membranes, and other structures

Two-dimensional views—therefore, several views from di erent angles are needed

Exposure to ionizing radiation for both patients and sta

Bulky and di cult-to-move equipment

Ultrasound

Basic principles

Based on sound waves transmitted from, and received by, the US transducer

Transducers contain a piezoelectric crystal and when a current is applied across the crystal, it will expand and contract as the polarity of the voltage changes

The speed of sound in tissue varies and sound waves are re ected at di erent tissue interfaces

Sound absorption is directly proportional to the frequency of the US beam, and therefore, high-frequency probes give good resolution but lack penetration

The operator may use an in-plane or out-of-plane approach

A hyperechoic (brighter) image is seen at a tissue interface with di erent acoustic impedance, e.g. soft tissue to bone

A hypoechoic (darker) image is seen across tissues with similar acoustic impedance, e.g. muscle and fat

Advantages of ultrasound-guided interventions

Visualization of nerves, arteries, and veins

Real-time visualization

No ionizing radiation

Portability

Good resolution of MSK tissue, and therefore can be used for TPIs

Visualization of peripheral nerves has led to increasing use in regional anaesthesia and improved operator skills

Can see di usion of injectate without use of radio-opaque contrast

Uses less personnel and resources

Evidence of superiority for regional procedures, compared to landmark technique (precision and safety)

Safety and accuracy of USS guided procedures can be increased by the use of a nerve stimulator attached to the needle

Disadvantages of ultrasound-guided interventions

Cannot visualize past bone

Di culty with obese patients or increased tissue depth

Operator-dependent

Computed tomography

Basic principles

Three-dimensional imaging technique with rotating radiation beam

Produces several cross-sectional images

Advantages of CT-guided interventions

Excellent spatial resolution and soft tissue contrast

Low chance of vessel, nerve, or visceral injury

Useful in patients with complex or di cult anatomy

Reducing the body area scanned and intermittent scanning can reduce radiation

Shows precise location of needle tip and surrounding structures

Disadvantages of CT-guided interventions

Lack of space, facilities, or expertise

Higher doses of radiation for patient and sta

Cumulative radiation may be an issue if repeat injections are needed instead of a single diagnostic block

Oblique angle of injection or increased depth to skin surface may increase the di culty of the procedure due to needle placement di culty

Expense, skill, patient claustrophobia, availability of sta and equipment may be a hindrance

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15.4 Chemical neurolysis

Introduction

The purpose of chemical neurolysis is to cause an irreversible disruption to neural transmission. This should induce changes of Wallerian degeneration and produce long-lasting impact on the neural bres

The irreversible nature of the changes produced means that any S/Es caused by chemical neurolysis need to be carefully considered

Chemical neurolysis may occur in the context of di erent patient factors and anatomical locations, and a variety of agents/concentrations can be used

The advantage of some chemical neurolytic procedures is that a one-o procedure can provide a long duration of pain relief

Neurolysis can also be performed with surgery, RF, or cryotherapy

Patient factors

The patient will need to give informed consent prior to having a procedure involving neurolysis

The patient should have tried conservative strategies such as medications or temporary nerve blockade

Patient comorbidities, such as cardiac disease, clotting disorders, and others, may a ect the safety, potential S/Es, and patient tolerability

The procedure should be performed in an appropriately monitored environment and where potential complications can be managed

Chemical neurolysis is mostly used in a palliative care setting in patients with limited life expectancy

Location

Chemical neurolysis may be performed in the CNS or peripheral nervous system

Intrathecal neurolysis may be used in complex cancer pain management:

- Phenol or alcohol can be used, depending on the spread of the disease, given the hyperbaricity of phenol and the hypobaricity of alcohol
- S/Es may include dea erentation, neuropathic pain, motor or sensory loss, arachnoiditis, and bowel and bladder dysfunction

Commonly performed peripheral blocks using chemical neurolysis include:

- Coeliac plexus block to treat upper abdominal visceral pain, with success reported in pancreatic cancer management. Alcohol may be preferred to phenol due to its greater ability to di use into target tissues and lesser a nity for vascular tissues. Some clinicians prefer to use phenol as it is not painful when injected
- Superior hypogastric plexus blocks are used in managing gynaecological cancer pain

Agents used

Phenol—6–10% concentration

Alcohol—33–100% concentration

Glycerol—reports of relieving pain for trigeminal neuralgia

Ammonium salts—preferential e ect on C- bres, with minimal e ect on A- bres, but overall e cacy is questionable

Patient position

Patient position during the procedure will a ect the spread of the agent

It is recommended the patient stays in a certain position for around 45 minutes after the procedure, to allow the agent to a ect the speci c target structures

Post-procedure care

The patient should be monitored for S/Es, depending on the procedure, and given instructions on discharge

Patients should be reviewed post-procedure

Should the patient experience a signi cant degree of pain relief, medications such as opioids can be carefully downtitrated. After some neurolytic procedures, opioids can be decreased immediately by 30–50%

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15.5 Radiation and Ionising radiation (medical exposure) regulations

Introduction

Radiation is a serious risk factor, making it important to know the basic guidelines of radiology to ensure the safety of the operators, sta and patients

The rst uoroscopy device was developed by Thomas Edison and other scientists, and introduced in 1900

Physics

Radiation is the dispersion of energy through electromagnetic waves or particles

Radiation ionizes the atom by breaking o the electrons from their orbits—ionizing radiation consists of charged particles

Electromagnetic energy is a type of energy radiating at light speed in the form of sine wave

An X-ray is a typical electromagnetic radiation

X-rays have shorter wavelengths and higher frequencies, and have higher energy levels

Fluoroscopy

Fluoroscopy is a live imaging technique using X-rays

The components are: a radiography tube which provides the source of energy to produce X-rays; an attached lter which modi es the X-ray energy spectrum; a collimator that restricts the focus area; an anti-scatter grid reducing the number of photons scattering on the image receptor; an image receptor; and an image intensi er

Units used for radiation exposure and dose

Exposure units in Roentgen (R) and in SI units Coulomb/kg

Radiation absorbed dose (RAD) and in SI unit Gray (Gy)

100 RAD = 1 Gy

Radiation Equivalent in Man (REM) and in SI unit Sievert (Sv)

Sievert—quanti ed biological e ect of ionizing radiations

100 REM = 1 Sv

For X-rays, 1 Sv = 1 Gy

X-ray chest 0.02 mSv

CT abdomen/pelvis 11 mSv (550 X-ray chest)

Annual Maximum Permissible Radiation Doses (see Table 15.5.1)

Minimum target organ radiation doses to produce organ pathologic e ects (see Table 15.5.2)

T Annual maximum permissible radiation doses

	Gn	M
Thyroid	0.5	50
Extremities	0.5	50
Eye lens	0.15	15
Gonads	0.5	50
Whole body	0.05	5
Pregnancy (to fetus)	0.0005	0.5

Minimum target organ radiation doses to produce organ pathologic e ects

Eye lens (cataract)	200	2
Skin burns (acute)	300	3
Sterility	400	4
Skin (erythema)	500	5
Permanent alopecia	700	7
Whole body (haemopoietic failure) (4–6 weeks)	200–700	2–7

Factors a ecting X-ray quality

Penetration capability depends on X-ray energy, ltration, distance, and structure of the X-ray tube anode

X-ray energy can be increased by increasing the power supply (voltage)

Scattered radiation

Scattered rays from the primary substance; occurs as a result of collision of electrons

Secondary radiation occurs when scattered X-ray radiation passes through an object. The patient becomes the primary source of scattered radiation during exposure time

Fluoroscopy usage types

Continuous uoroscopy, which is the most dangerous in terms of radiation safety

High-speed uoroscopy, used where normal uoroscopy is inadequate

Pulsed uoroscopy, with image speed and frames per second rate; the most preferable format

E ects of radiation

1. Direct (de nitive/deterministic) e ect: evident with the result of dying cells. It can occur with high linear energy transfers (LETs) and the ratio of dying cells increases with increased radiation doses. Associated with cataract, infertility, hair loss, and skin issues
2. Indirect (cytoplastic/stochastic) e ect: the severity of the e ects is unrelated to the dose of radiation exposure. It can occur with low LETs via production of free radicals, and doses used for radiation are additive. Cytoplastic e ects of radiation may cause mutagenic e ects such as cancer and leukaemia. Radiation causes neuroplasticity, which initiates DNA damage. Cancer risk is higher at extremes of age and in females
3. Acute e ect: can occur within hours to days after high doses of radiation exposure, even for a brief period, causing cell death
4. Haemopoietic cells are the most a ected by radiation exposure as they have a replication rate, followed by cells of the reproductive system, then the GI system, and lastly by nerves and muscles

Radiation safety

There are three basic rules to be considered for radiation protection: time, distance, and use of protective material.

Hold the X-ray tube low: the X-ray tube should be kept under the table or patient, so that the scattered beam is pointed downwards

DAP and screening time

	DAP (Gy m^2)	Screening time (min)
Lumbar medial branch blocks	2.5	60
Sacroiliac joint injection	1.63	43

To keep away from the source of radiation: one should stand 3m away from the table to reduce the beam level

Consider the scattering pro le: using thyroid-protective lead and special lead-sided protective glasses may protect from scattered beam

Wear protective lead

Track the beam dose and time. The dose–area product (DAP) and screening time should be kept to a minimum. There are no standards, but a rough guide, for example, could be as mentioned in Table 15.5.3

Save the last image

Use the pulse mode, rather than continuous screening

Limit the beam size (collimation)

The source should be close to the object to reduce scatter; avoid magni cation

The device should undergo regular technical checks

Personal radiation measurement devices

Dosimeters are devices carried by personnel who work with radiation to determine radiation exposure—best worn on the chest pocket under the apron

IRMER (Ionising Radiation (Medical Exposure) Regulations 2017)

The main aim is to achieve exposure 'as low as reasonably practical' (ALARP)

Practitioner—takes responsibility/justi cation for individual exposure

Operator—is responsible for the delivery of radiation and its practical aspects

Referrer—is responsible for providing adequate medical information to the practitioner to help them decide whether the necessary radiation exposure will be bene cial or not

Summary

Fluoroscopy is a highly essential technique for interventional pain procedures; however, it can bring many risks and dangers with it

One must be very careful when using uoroscopy, used for the shortest possible time and ALARP

All pain physicians should have radiation safety training and all exposure should always be justi ed

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15.6 Radiofrequency denervation

Introduction

Kirschner introduced percutaneous current lesions in 1931 for the treatment of patients with trigeminal neuralgia

Its use became further established in 1950s and 1960s

Physics

The RF voltage from the generator is set up between the (active) electrode and the (dispersive) ground plate, which is placed on a non-hairy part of the body

RF current ows through the tissue, resulting in an electric eld through the circuit completed within the body

This creates an electric force on the ions in tissue electrolytes, causing them to oscillate at a high rate

Frictional dissipation of the ionic current within the uid medium causes tissue heating, producing a lesion

Mechanism of action

The heat generated in the nerve cells at the electrode tip causes coagulation, which is believed to interrupt pain conduction

Large lesion size is known to improve e cacy. This depends on the diameter of the electrode and the length of the uninsulated electrode tip

Technique

The RF needle is placed under uoroscopic guidance, with the tip lying parallel and adjacent to the nerve tissue in order to create the largest lesion

Cooled RF and Trident needles have an end-on needle position

Indications

Percutaneous cervical cordotomy:

- In unilateral, incident, and/or neurogenic pain in advanced cancer patients
- Lateral approach through the C1–C2 intervertebral space: a 22G RF needle with a 2 mm active tip is placed in the spinothalamic tract in the spinal cord, followed by sensory (cold or warm sensation) and motor stimulation and RF ablation
- An RF lesion is made, resulting in a tip temperature of 90°C for 10 seconds

Trigeminal neuralgia:

- In drug-resistant cases and where microvascular decompression is not indicated or not possible
- A 22G RF needle with a 2 mm active tip is placed in the foramen ovale through the cheek musculature

A sensory stimulation threshold below 0.2 V is achieved and an RF lesion of 60–65°C for 60 seconds is made. Long-term success rates vary from 80% to 90%

Anaesthesia dolorosa has made balloon decompression a preferred option

Cluster headache:

Sphenopalatine ganglion RF ablation is performed by laterally placing the needle through the triangle formed by the zygoma and the muscular and articular processes of the mandible

Paraesthesiae should not be felt at <1.0 V and an RF lesion is achieved at 80°C for 60 seconds

In episodic cluster headache, complete pain relief has been achieved in 60% of patients, and in chronic cluster headache in 30% of patients

Lumbo-sacral pain:

Following a positive medial branch block for facet joint pain, an 18G RF needle with a 10 mm curved tip is placed in a caudal to cranial and a lateral to medial position, with an angle from the midline of 60° at the junction of the transverse process and the superior articular process

After advancing the RF needle to the posterior foraminal line, motor stimulation is used (<1 V) to con rm multi dus stimulation and no radicular stimulation

An RF lesion is obtained at 80°C for 60 seconds, and the needle rotated to repeat the lesion

Extensive literature has led the Spine Intervention Society (SIS) and the National Institute for Health and Care Excellence (NICE) to recommend RF denervation for pain relief of 12 months or longer. The NNT is between 1.1 and 1.5

For SIJ denervation, a palisade technique of multiple needles or a single needle (Simplicity™ RF cannula) is used to create a lesion at the lateral border of the S1, S2, and S3 foramen for the lateral branches of the corresponding dorsal rami, along with an L5 dorsal ramus lesion

Cervical facetogenic pain and cervicogenic headache:

Following a positive medial branch block, a 22G or 18G RF needle with a 5 mm or 10 mm active tip is placed under uoroscopic guidance parallel to and on the articular pillar (across the C2–3 facet joint for the third occipital nerve)

Several RCTs and well-designed studies have demonstrated pain relief of up to 422 days in over 70% of patients

Abdominal pain:

A splanchnic RF lesion is created at T12 or L1 after a positive diagnostic LA injection

A 20G, 15 cm, RF needle with a 10 mm active tip is placed overlying the side of the vertebral body at the junction of the lower and middle third of the vertebra, after the spinous processes are projected over the facetal joint column on the opposite side

The needle tip is advanced to the anterior border of the vertebral body

Following sensory stimulation of up to 2 V, an RF lesion is created at 80°C for 60 seconds

Lower limb pain with autonomic dysfunction:

Lumbar sympathetic ganglion RF is performed at L3 and L4 levels in a fashion similar to splanchnic RF

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15.7 Pulsed radiofrequency

Introduction

First PRF procedure performed on a lumbar DRG in February 1996

Physics

PRF applies short pulses of RF signals from an RF generator to the tissue through an insulated needle with an exposed active tip of 5 mm or 10 mm

A commonly used sequence is a pulse frequency of 2 Hz and a pulse width of 20 ms per 500 ms, permitting 480 ms of silent phase

The RF oscillation frequency is about 420 kHz, which is the same as for conventional RF

In PRF, because the pulse duration is only a small percentage of the time between pulses, the average tissue temperature rise for the same RF voltage is much less and the production of heat during these pulses depends on the power deposition

Higher voltages can be applied to the electrode in PRF than are commonly used in RF without raising the average tissue temperature into the denaturation range of above 45°C

However, as the electric elds wane rapidly with increasing distance from the tip, there is very little destruction to the tissue

Mechanism of action

Neuromodulatory e ect by alteration in synaptic transmission

The low frequency of pulses and high voltages induce long-term depression of synaptic transmission at the spinal cord, and antagonizes the long-term potentiation that leads to chronic pain states

Ion channel disruption and resting and threshold potential alterations are other possible e ects

Technique

A needle is placed under image guidance, with the exposed tip adjacent to the neural tissue

Indications

Radicular pain:

PRF was compared to conventional RF at 42°C for patients with lumbo-sacral radicular pain. The global perceived e ect was signi cantly better in the PRF group

In a prospective cohort study of 65 patients, the reduction in NRS and Oswestry Disability Index was statistically signi cant, compared to the baseline

Cervical DRG was studied in one RCT and PRF was shown to be more e ective than placebo at 3 months' follow-up

In two observational studies, it had >50% pain reduction in >60% of patients. This e ect appeared to be sustained at 1-year follow-up

PRF adjacent to the cervical DRG is recommended due to the high risk of transforaminal steroids in the cervical region

It could be considered for the treatment of lumbo-sacral radicular pain

Trigeminal neuralgia:

PRF of the Gasserian ganglion could be an alternative, with fewer S/Es; unlike conventional ablative treatments that can cause anaesthesia dolorosa or hypoaesthesia

The duration of e ect may be somewhat shorter than that of conventional RF; however, repeat intervention seems to have comparable results as the initial one

Occipital neuralgia:

In an RCT of 81 patients, pain reduction was signi cantly greater in the PRF group, compared with the steroid group; this persisted through the 6 months' follow-up. S/Es were minor and transient in both groups, which makes PRF a useful option

Shoulder pain:

In three RCTs and four observational studies, treatment lasted for 6 months. The e ect of PRF on the suprascapular nerve was better than that of sham intervention and comparable to TENS

Knee pain:

Intra-articular, DRG, and peripheral nerve (femoral, saphenous, common peroneal, tibial) and plexuses (peripatellar, subsartorial, and popliteal) have been studied and the results are mixed

PRF of sensory nerves should be preferred for the treatment of neuropathic pain, while avoiding neuroma formation and dea erentation pain induced by ablative techniques

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CHAPTER 16

Head and Neck

Ann-Katrin Fritz and Jan Rudiger

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16.1 Cranial nerves

Importance of good anatomical knowledge

Basic functions of cranial nerves (CNs)

Examination techniques of CNs

To assess and treat pain conditions involving CNs

Olfactory nerve (I)—sensory

Function: smell

Test with co ee and cinnamon

Optic nerve (II)—sensory

Function: vision (via retina and optic disc)

Test: visual acuity, colour, elds; light and accommodation re ex; fundoscopy

Oculomotor nerve (III)—motor, parasympathetic

Function: movement of eyeball (inferior, medial, and superior via inferior, medial, and superior rectus muscles, inferior oblique muscle), eyelid movement (levator palpebrae superioris muscle)

Parasympathetic preganglionic bres: accommodation and pupillary light re exes (via pupillary sphincter and ciliary muscles from the Edinger–Westphal nucleus)

Test: gaze, accommodation, rule out double vision

Trochlear nerve (IV)—motor

Function: motor movement via the superior oblique muscle (to depress and internally rotate the eyeball)

Test: eye movement (vertical diplopia, worse when looking down and inwards), head tilt (away from a ected side)

Clinical relevance: microvascular damage (diabetes, hypertension), congenital, thrombophlebitis of sinus cavernosus, raised ICP

Trigeminal nerve (V)—largest cranial nerve with three divisions, mixed

Ophthalmic nerve (V1)—sensory:

Function: sensation to superior face and anterior scalp

Test: touch to forehead on each side with cotton wool

Additional test: corneal re ex (a erent component)

Maxillary nerve (V2)—sensory:

Function: sensation to midface, including maxillary sinus, upper teeth, and gum

Test: touch to cheeks with cotton wool

Mandibular nerve (V3)—sensory + motor:

Function: sensation to lower face, including lower teeth and gums

Test: touch to cheeks with cotton wool

Additional test: temporalis and masseter muscle function (bulk, ability to open the mouth against resistance and jaw jerk)

Clinical relevance:

Trigeminal neuralgia (usually unilateral) or MS (can be bilateral)

Abducens nerve (VI)—motor

Function: motor supply of lateral rectus muscle

Test: eye abduction

Facial nerve (VII)—mixed

Function: facial expression, taste, salivation, lacrimation, corneal re ex

Sensory (taste): anterior two-thirds of the tongue (via chorda tympani)

Motor supply to orbicularis oculi, ear muscles, buccinator muscle, lips, chin, and platysma

Parasympathetic bres to salivary and lacrimal glands and mucosal glands

Test: try to open the eyes against active lid closure, showing the teeth, creasing up the forehead, pu out the cheeks against resistance, corneal re ex (e erent part)

Clinical relevance: Bell's palsy

Vestibulocochlear nerve = auditory nerve (VIII)—sensory

Function: hearing and balance

Test: sound (snapping ngers next to the ear; Weber's and Rinne's tests)

Clinical relevance: neuro bromatosis type 2

Glossopharyngeal nerve (XI)—mixed

Function: sensation, taste, motor, carotid body and sinus, parotid gland

Sensory: pharynx, tonsils, soft palate, and posterior third of the tongue

Taste: posterior third of the tongue

Motor: stylopharyngeus muscle

Parasympathetic: parotid gland

Test: gag re ex

Clinical relevance: glossopharyngeal neuralgia

Vagus nerve (X)—mixed

Function: sensory, taste, autonomic

Sensory: external ear, larynx, pharynx, taste between the epiglottis and the tongue

Motor: vocal cords via recurrent laryngeal nerve (left side crosses the aortic arch), most muscles of the larynx and pharynx, and smooth muscles of GI tract

Parasympathetic supply to thoracic and abdominal visceral organs (cardiac, pulmonary, gastric, hepatic, and coeliac plexus)

Test: swallowing, speech, and symmetry of the uvula

Clinical relevance: vagal nerve stimulation for treatment of cluster headaches

Accessory nerve (XI)—motor

Function: motor supply to sternocleidomastoid and trapezius muscle

Test: shrugging the shoulders and turn the head against resistance

Clinical relevance: torticollis (neurovascular compression), winging of the shoulder blade, and secondary shoulder pain

Hypoglossal nerve (XII)—motor

Function: motor supply to intrinsic and extrinsic tongue muscles (except palatoglossal muscle)

Test: tongue muscle wasting, fasciculation, and symmetry

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16.2 Anatomy of the trigeminal nerve and trigeminal ganglion block

Anatomy of the trigeminal nerve (fth cranial nerve)

Largest cranial nerve with large sensory and small motor roots

Majority of sensory supply to the face, orbit, nose, and mouth

Three divisions (V1 and V2—purely sensory; V3—sensory and motor)

Each division has parasympathetic bres to glands

Trigeminal ganglion = Gasserian ganglion

V1—ophthalmic branch

Through the superior orbital ssure

Branches: frontal, lacrimal, nasociliary

Sensory: forehead and scalp, upper eyelid, conjunctiva + cornea, frontal and ethmoid sinuses, dorsum of the nose (small branches to the dura)

Parasympathetic: lacrimal gland

V2—maxillary branch

Through the foramen rotundum (posterior to the pterygopalatine fossa)

14 terminal branches

Sensory: lower eyelid and conjunctiva, cheeks, maxillary sinus, nasal cavity and lateral nose, upper lip, upper teeth + gingiva, superior palate

Parasympathetic: lacrimal gland, nasal glands

V3—mandibular branch

Through the foramen ovale

Four terminal branches: buccal, inferior alveolar, auriculotemporal, lingual

Sensory: mucosa and oor of oral cavity, external ear, lower lip, chin, lower teeth and gingiva, sensation to anterior two-thirds of the tongue (taste via chorda tympani of the facial nerve)

Parasympathetic: parotid, submandibular, sublingual glands

Motor supply: muscles of mastication (masseter, temporal, medial, and lateral pterygoid muscles) and tensor veli palatini, tensor tympani, mylohyoid, and anterior belly of digastric muscles

All three branches

All three divisions form the trigeminal ganglion (Gasserian ganglion), which lies on the oor of the middle cranial fossa of the skull

The trigeminal nuclear complex is located in the midbrain, pons, medulla, and upper cervical cord as far as C4

Three sensory trigeminal nuclei (spinal nucleus—pain conduction), one motor nucleus (lies in the pons)

1st ON: noxious stimuli to the face main trigeminal nuclei and spinal nucleus (clenching of jaw, chattering of teeth)

2nd ON: spinal nuclei—crosses the midline thalamus (trigeminal thalamic tract) (vulnerable to pressure at the edge of the dura mater, e.g. meningioma, trauma)

3rd ON: thalamic nuclei somatosensory cortex, insula, cingulate cortex

Trigeminal ganglion block

Indications

Trigeminal neuralgia (tic douloureux)—therapy-refractory

Atypical trigeminal neuralgia

Intractable chronic cluster headaches

Herpes zoster

Chronic idiopathic facial pain

Cancer-related pain palliation

Contraindications

Patient refusal

Increased ICP

Local or systemic infection

Coagulopathy, thrombocytopenia, or inability to stop anticoagulation drugs

Distorted or complicated anatomy

Immunocompromised patients (e.g. facial malignancies) high risk of infection

Untreated severe psychopathology

Patient preparation and positioning

Anaesthetic assessment as conscious sedation is required

Review of potential anticoagulation drug use or possible risk of thrombocytopenia or coagulopathy

Patient positioned supine, with head on radiolucent head ring, with IV access and full Association of Anaesthetists of Great Britain and Ireland (AAGBI) monitoring

Conscious sedation by anaesthetic colleague with supplemental oxygen

Prophylactic antibiotic administration may be indicated to reduce risk of meningitis

Technique (PRF/RF lesioning)

Skin preparation, with ipsilateral eye closed and careful draping

Posteroanterior (PA) view with square nasal septum

25–30° caudal tilt for submental view

Oblique ipsilaterally by 20–30° to get the foramen ovale into view just medial to the ramus of the mandible (lemon-shaped)

Mark skin entry point about 2 cm lateral to the angle of the mouth

Anaesthetize the skin with a 25G needle and lidocaine

Gradually advance a 10 cm 22G RF needle with a 5 mm straight tip towards the foramen ovale, with intermittent uoroscopy

Once the needle is engaged in soft tissue, change to lateral view for depth indication

Further advance the needle to aim for the angle produced by the clivus and petrous portion of the temporal bone

Recheck the oblique view to con rm the needle advancing towards the medial or middle third of the foramen ovale

Advance the needle through the foramen ovale on lateral view, making sure the needle tip stays below the clivus

Remove the stylet and aspirate

CSF leak may occur if the dural layer surrounding the ganglion is pierced with a sharp needle and the tip positioned in the trigeminal cistern; this will need repositioning only if injection of medication is planned

Reposition the needle if blood occurs—abort the procedure if blood is aspirated despite repositioning of the needle twice

Thermal rhizotomy

Sensory test at 100 Hz 0.1–0.5 V (elicits paraesthesiae in a ected area)

Motor test at 2 Hz up to 2 V—mandibular contractions (motor branch)

1 mL of LA ± 2 mg of dexamethasone—wait for 1 minute

Lesioning at 60°C with sedation for 60 seconds

Recheck sensory response and also corneal re ex (V1) in awake patient

Repeat in 5°C increments to a maximum of 80°C

Complications

Bleeding

Retrobulbar haematoma

Meningitis

Local infection
High spinal (if LA injected)
Anaesthesia dolorosa up to 4%
Corneal anaesthesia, hypoaesthesia, keratitis, and ulceration
Masseter weakness after lesioning of V3

Additional information

Sensory loss of the treated division is to be expected as a S/E in up to 98% (needs to be explained to the patient and documented prior to chemical or thermal lesioning)
Injection of LA despite a CSF leak could lead to a high spinal block
If masseter contraction is seen on motor testing, the needle may be advanced a bit further (check lateral view) prior to RF lesioning
Avoid entering other foramina: inferior orbital ssure (superiorly), foramen lacerum with carotid artery (postero-medially), and jugular foramen and carotid canal (postero-inferiorly)

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16.3 Sphenopalatine ganglion block

Anatomy of the sphenopalatine ganglion (SPG) = pterygopalatine ganglion

Large extracranial ganglion (5 mm in size) located in the pterygopalatine fossa (1 cm-wide and 2 cm-high pyramidal structure)
Complex neural centre, parasympathetic ganglion
E erent portion of the trigeminal autonomic re ex

Sensory supply

Two sphenopalatine branches of the maxillary nerve supply the SPG; most bres pass directly into the palatine nerves, while a few enter the ganglion

Sympathetic supply

Post-ganglionic bres come from the superior cervical ganglion via the carotid plexus and deep petrosal nerves and the greater petrosal nerves to the SPG

Parasympathetic supply

Preganglionic innervation comes from the superior salivary nucleus of the facial nerve in the pons through the greater petrosal nerve
In the SPG, the preganglionic bres synapse with the post-ganglionic bres

Post-ganglionic fibres (vasodilator and secretory fibres) travel with the deep branches of the maxillary trigeminal nerve to the mucosa of the nose, soft palate, tonsils, uvula, roof of the mouth, upper lip and gums, and upper part of the pharynx

Post-ganglionic fibres via the maxillary trigeminal nerve to the nasal, palatine, and pharyngeal glands

Further post-ganglionic fibres via the zygomatic nerve and lacrimal nerve (ophthalmic nerve) to the lacrimal gland

Branches of the SPG

1. Orbital branches (ethmoid and sphenoidal sinuses, mucosal glands)
2. Posterior superior and inferior nasal branches (nasal cavity and glands, upper part of the septum)
3. Nasopalatine nerve (frontal part of the palate, palatine glands, and mucosa of the upper incisors and canines)
4. Greater and lesser palatine nerves (nasal cavity; gums, mucosa, and glands of the hard and soft palate)
5. Pharyngeal nerve (pharyngeal mucosa and glands)

Indications for SPG block

Potential benefits must outweigh risks due to the invasive nature of the procedure

Intractable, medically resistant pain to conventional treatment (e.g. medication, Botox® injections, greater occipital nerve (GON) block) for:

- Cluster headache, chronic persistent migraine, trigeminal autonomic cephalgias
- Intractable orofacial pain syndromes and atypical facial pain
- Herpes zoster in the ophthalmic division of the trigeminal nerve

Contraindications

Patient's refusal or inability to obtain consent

Localized or systemic infection

Coagulopathy or thrombocytopenia

LA allergy

Distorted or complicated anatomy (e.g. after surgery, infection)

Immunocompromised patients (facial malignancies) due to high risk of infection

No clear causation between anatomy and symptoms

Patient preparation and positioning

Consent, including detailed explanation of all potential complications

Review medication, and rule out anticoagulation and potential allergies to skin prep and injectate

Examine the area of injection for potential infection

IV access, full monitoring, trained assistant, and resuscitation equipment

Positioning: supine with head ring, head in the C-arm

Technique (infra-zygomatic anterior or coronoid approach) under fluoroscopy

Described is the infra-zygomatic approach; alternatives are the transnasal approach (used in ear, nose, and throat (ENT) surgery with topical 4% cocaine) and transoral approach (often used by dentists)

Fluoroscopy: start in the lateral view to identify the maxilla, lateral pterygoid plate, and coronoid notch—ensure the pterygoid plates are overlapped

Skin entry point is just inferior to the zygomatic arch either through the coronoid notch (transcoronoid approach) or anterior to the mandible (anterior approach)

Mark the skin entry point; anaesthetize with a 25G hypobaric needle and 1% lidocaine, and position a 90 mm 22G spinal needle in tunnel vision

Immediate lateral view to check the depth as the needle is being advanced towards the lateral nasal wall

Aspirate and inject 0.1–0.2 mL of contrast agent under live screening to outline the pterygoid fossa and exclude intravascular placement

Inject 1–2 mL of 0.25–0.5% levobupivacaine with non-particulate steroid

Monitor the patient carefully post-operatively for 40–60 minutes for bleeding and neurological de cit

Complications

Epistaxis due to piercing of the lateral nasal wall

Intravascular injection, bleeding, and haematoma (cheek most common) injury to maxillary artery or branches

Infection (especially if nasal or oral mucosa pierced)

Re ex bradycardia during RF lesioning (parasympathetic bres in the SPG)

Facial numbness and paralysis

Double vision (spread of LA to the abducens nerve via the inferior orbital ssure)

Dry eye (especially with neuroablation; often temporary)

Fever

Flare-up of symptoms

Shift of headache side

Additional information

RF ablation can be performed in cancer pain, intractable headache, and facial pain syndromes

Neuroablation techniques are only feasible with the infra-zygomatic approach

Aspiration of air means the needle tip is too advanced into the nasal cavity

Limit injectate to 1–2 mL to avoid spread of LA into the abducens nerve

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16.4 Greater occipital nerve, minor occipital nerve, and third occipital nerve

Anatomy—introduction

Cervico-trigeminal nucleus—pain of occipital neuralgia/cervicogenic headaches is referred to structures innervated by the trigeminal nerve, including the eyes, temples, and forehead, due to the C1–3 origin of the occipital nerves that share a relay station in the brainstem with the trigeminal cell bodies

Occasionally, there can be a connection between the greater and lesser occipital nerve

Greater occipital nerve

Receives bres from the dorsal primary rami of the second cervical nerve roots

Exits the C2 foramen laterally to cross over the inferior oblique muscle at the level of the atlanto-occipital joint

Pierces the semispinalis muscle and the lateral edge of the conjoined tendon on its ascent to the superior nuchal ridge at which point the occipital artery runs just lateral to it

Sensory innervation to the medial portion of the posterior scalp

Location is variable with 5–28 mm from the midline, and the GON is medial to the occipital artery

Lesser or minor occipital nerve (LON)

Receives bres from the posterior rami of the second and third cervical nerves

Travels along the border of the sternocleidomastoid muscle as part of the super cial cervical plexus

Sensory innervation of the lateral portion of the posterior scalp, including the postero-superior surface of the pinna of the ear

Can have an anomalous origin from the trunk of the suprascapular nerve

Third occipital nerve (TON)

Medial sensory branch of the posterior division of C3, which supplies the midline of the occipital region (medial to the GON) and innervates the C2/3 facet joint

Supplies proprioceptive bres to the semispinalis muscle

Susceptible to acceleration–deceleration trauma together with the C2/3 joint

Indications

Occipital neuralgia (entrapment or injury to occipital nerves):

- Shooting or stabbing pain in cranial portion of the neck with or without a referral pattern to the occiput, temples, forehead, and retrobulbar area (allodynia, paraesthesiae, and numbness)
- Impairment of vision and ocular pain (67%), tinnitus (33%), dizziness (50%), nausea (50%), and congested nose (17%) can be present (connection with CN VIII, IX, and X, and cervical sympathetic plexus)
- Examination: tender to pressure over course of the nerves, positive Tinel's sign, diagnosis con rmed by diagnostic nerve block

History of whiplash injury or similar trauma

Medication-refractory migraine-type headache

Cluster headache

Contraindications

Patient refusal
Localized or systemic infection
Coagulopathy or thrombocytopenia
Distorted or complicated anatomy such as Arnold–Chiari syndrome, cervical instability, or acute fracture

Patient preparation and positioning

Full monitoring ± IV access (risk of bradycardia)
Seated position, neck flexed, with head supported on the hands
Prone if fluoroscopy-guided, with pillow under the chest to allow head flexion
Skin prepared with appropriate agent

Injection technique (GON)

Landmark technique

Palpate the occipital nuchal ridge in the midline and inject perpendicularly with a 23G needle after careful aspiration at a point that is 2 cm lateral and 2 cm inferior to that point

Fluoroscopy-guided

No longer commonly used due to advances in US; however, may be preferable in whiplash patients with cervicogenic headache
LON block at C2/3 level
PRF considered if LA infiltration does not provide sufficient analgesia
Injection of botulinum toxin is controversial unless part of PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) which may relieve muscle tension

Ultrasound-guided

Linear probe
Identify the bifid C2 spinous process with a horizontal probe position, then move laterally with the medial border of the probe still over the C2 spinous process and the lateral border of the probe towards the C1 transverse process
The GON crosses the inferior oblique muscle (on top of it) and lies underneath the semispinalis capitis muscle

Complications

Haematoma
Infection
Temporary dizziness, gait disturbance, discomfort at injection site, headache
Mild ataxia and unsteadiness due to loss of tonic neck reflexes
Alopecia and skin atrophy
Intravascular injection, bradycardia
Total spinal or brain injury if skull defect present and needle passes through (cave: trauma patients)

Additional information

Subcutaneous occipital nerve stimulation has shown good results in refractory occipital neuralgia
Warn the patient about potential numbness around the occiput and upper neck plus dizziness

Apply pressure over the injection site for a few minutes to reduce the risk of haematoma
Observe the patient for at least 10 minutes before discharge
Hypoaesthesia is not required for headache relief
Patients should not drive a car until any signs of ataxia and unsteadiness have resolved
Patients with a history of posterior fossa surgery or blunt trauma to the occiput may have a skull defect which may lead to injection intracranially, resulting in brain injury or a total spinal block
Lasting bene t for occipital neuralgia or cervicogenic headache requiring a series of injections
Better outcome may be achieved in combination with pharmacotherapy and physical therapy
Persistent pain that only responds brie y to a GON block may bene t from Botox A, PRF of the GON, RF lesioning of the GON, or prolotherapy

Further reading

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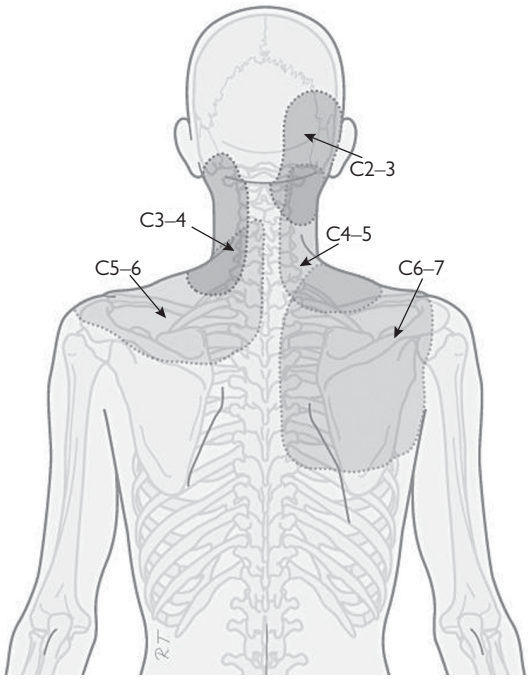
16.5 Cervical facet joint/medial branch blocks and radiofrequency denervation

Cervical facet joint pain

Neck pain is common
Prevalence of facet joint-related neck pain reported as 25–65% (possibly over 50% of patients attending the pain clinic for neck pain, more common than lumbar facet joint pain)
Pain referral pattern from cervical facet joints: C2/3—into the occipital aspect of the head as cervicogenic headache; C3/4 and C4/5—between the base of the skull and the rst thoracic vertebra over the postero-lateral aspect of the neck to the medial aspect of the shoulder girdle; C4/5 and C5/6—referred to the shoulder girdle and upper part of the scapula; C6/7—over the scapula (see Fig. 16.5.1)
Cervical facet joint syndrome: axial neck pain, tenderness on palpation of the posterior paravertebral cervical areas, pain and limitation of extension and rotation, absence of neurological symptoms in the arms

History

Exclude red ag symptoms (e.g. malignancy, myelopathy, instability/trauma, vertebral artery insu ciency, immunocompromise)
Pain mostly unilateral and not past the shoulder
Rotation and retro exion are usually painful and limited



Radiation pattern of cervical pain

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Examination

Rotation in neutral position—entire cervical column

Rotation in forward exion—higher cervical segments

Rotation in retro exion (head extension)—lower cervical segments

Palpation—local tenderness over facet joints (pressure of at least 4kg)

If neck pain is accompanied by shoulder pain, exclude shoulder pathology

Investigations

X-ray, CT, MRI (tumour, infection, fracture, degeneration, facet sclerosis, osteophytes)

Diagnostic cervical facet joint injections or medial branch block (MBB) regarded as successful if >50% pain relief when a ected levels are injected (to proceed with RF denervation)

Anatomy of cervical facet joints

Comprises the joints from C2/3 to C7/T1 at an angle of 45° with the longitudinal axis through the cervical spine

Cervical facet joints have <1 mL volume

Higher density of mechanoreceptors, compared to lumbar facet joints

Pairs on each side formed by the inferior articular process of the superior vertebral segment and the superior articular process of the inferior vertebral segment

Allows extension, exion, and rotation

Innervation by the medial branches of the dorsal rami above and below the joint

C2/3 joint also supplied by the third optical nerve, which, like the C3 medial branch, originates from the C3 dorsal ramus

The medial branches are bound by fascia and cross around the waist of the articular processes of the respective numbered vertebra

At C7, the medial branches are located higher than at C3–C6, due to the transverse process, and 70% are located across the C6/7 facet joint

Indications

Arthritic or traumatic chronic neck pain, cervicogenic headache, suboccipital headache, axial neck pain, and/or upper thoracic pain

Neck pain and/or headache with neck movements: exion, extension, and rotation

Pain intensity >5/10 and functional disability (neck disability index)

Failure to respond to conservative management, including physiotherapy, postural optimization, and pharmacotherapy

Contraindications

Infection

Inability to consent

Anticoagulation, antiplatelet therapy, or coagulopathy

Pregnancy

Needle phobia

Severely distorted anatomy

Patient preparation and positioning

Informed consent (full explanation of potential complications)

Examination for con rmation of extent of disease, recent average pain score (baseline), and exclusion of infection

Review for potential bleeding risk (cervical area more vascular than lumbar area)

IV access and full monitoring

Exclusion of allergies to drugs, skin prep

Positioning depends on patient ability and preference of practitioner (supine and lateral for diagnostic blocks; lateral or prone may be preferred for denervations with a posterior approach)

Technique

Medial branch blocks

Two cervical medial branches must be blocked for each facet joint (above and below the joint)

Posterior or lateral approach to reach crossing = centre points of the waist of the articular pillar, with the exception of the third optical nerve

Lateral approach (most suited for C3–6): with patient in supine position and the head on radiolucent head ring; identify articular pillars on lateral view

Aim for the spine on screen horizontally, with the head on the left, shoulders on the right, and cervical spinous processes heading downwards

Avoid any double shadows and adjust C-arm accordingly in all planes

Super cial SC in ltration of LA with a 25G needle and insert a 50 mm spinal needle from postero-laterally towards the centre of the rectangle of the articular pillar and bony contact

Con rm position on anteroposterior (AP) view—the needle tip should sit in the groove

Inject 0.25 mL of LA, with or without non-particulate steroid, at each level after careful aspiration

Assess e cacy of block within 10–20 minutes of block, and document

Mean duration in a study: 14–16 weeks (3.5 injections per year)

Radiofrequency denervation

After successful, but short-lasting medial branch blocks

Posterior approach preferred for better lesion size, but particularly for lower C6/7 denervation—patient in lateral or prone position

Start with AP view to aim for groove or waist of articular pillars

Insert a 5 cm 22G needle with a 3–5 mm active straight tip slightly more caudally (one level below) for a slightly tangential approach to the medial branch

Position as per MBB (centre of the rectangle) and check needle position is posterior to the neural foramen on lateral view

Aim for impedance of 300–500 Ohm (higher = periostium; lower = intravascular)

Perform sensory testing at 50 Hz and motor testing at 2 Hz in awake patient

Aim for sensory response at <0.5 V and negative motor response (triple the sensory threshold) prior to injection of 0.25 mL of LA and lesion at 80°C for 1 minute

Inject 0.5 mL of LA with non-particulate steroid (e.g. dexamethasone) after the lesion to reduce post-procedural discomfort unless contraindicated

Complications

Infection

Bleeding

Neural trauma—especially nerve root damage

Dural puncture

Spinal cord damage

Weakness or numbness in the arms (usually temporary)

Dizziness, ushing, sweating, nausea, hypotension, vasovagal reaction, syncope

Headaches

Flare-up of pain, especially with denervation

Additional information

Atlanto-occipital and atlanto-axial joints are anterior joints and not considered facet joints

Ideally perform two diagnostic test blocks with low volume (0.25 mL) prior to denervation

Some clinicians recommend two diagnostic blocks (to decrease the number of false positives, but increased false negatives), and others just one diagnostic block (decreased burden for patient with repeated injections, very few negative responses)

Higher volumes of LA may hamper adjacent sensory test in denervation or give false positive results in diagnostic MBBs

Do not denervate bilaterally at the same sitting due to the risk of drop head syndrome

Do not denervate if the needle tip is positioned too close to the neuroforamen and without negative motor test (i.e. no widespread neck, shoulder, or upper limb movement on motor stimulation)

The needle must never lie anterior to an imaginary line passing through the posterior margin of the intervertebral foramen

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CHAPTER 17

Thorax and Abdomen

Shyam Balasubramanian, Laura Beard, Mohamed Dorgham, Rahul Guru, Doug Stangoe, and Ali a Tameem

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17.1 Thoracic facet joint/medial branch blocks and radiofrequency denervation

Anatomy

Facet joints are synovial joints with a true joint capsule and are one of the weight-bearing structures in the vertebral column

Each facet joint is formed by the articulation of the superior articular process of the vertebra below and the inferior articular process of the vertebra above

The thoracic facet joints are steeply angulated to the axial plane (60–70°) and at 20–30° from the frontal to the sagittal plane

The superior and inferior articular processes of the thoracic spine cannot be identi ed separately

Innervation: the dorsal ramus at each level gives o a medial branch, which supplies the facet joint at the same level and the facet joint below. Therefore, each facet joint receives innervation from the dorsal ramus at the same level and from the level above

The medial branch crosses the superolateral corner of the transverse process (TP) and then passes medially and inferiorly

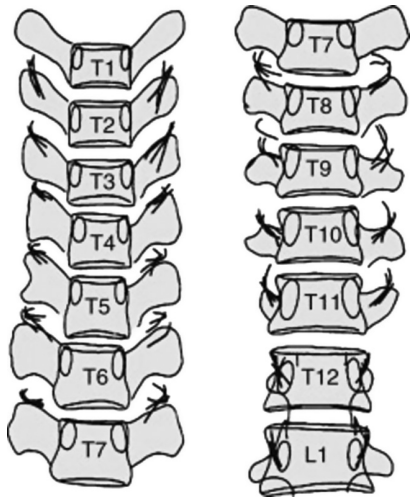
At the mid-thoracic level (T5–T8), an in ection occurs superior to the superolateral corner of the TP

See Figure 17.1.1

Indications

Diagnostic block with LA to predict whether RF lesioning will provide long-lasting pain relief in conditions causing thoracic spinal pain (dull or sharp, aching, and usually radiates anteriorly across the chest)

These conditions include: arthritis, in ammation, trauma, acceleration–deceleration injuries, and osteoporotic or osteolytic vertebral fractures



Courses of the thoracic medial branches across the transverse processes of the vertebrae

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Contraindications

Similar to other interventions

Patient preparation and positioning

Standard protocol followed

The patient is positioned prone, with pillows under the chest. This allows for exion of the thoracic spine

The C-arm is aligned to obtain an AP view of the thoracolumbar region and the target level is identi ed by counting the corresponding rib either from the thoracolumbar region (T12) upwards or from T1 downwards

Medial branch block

Once the thoracic medial branch level to be block is located, the endplate of the vertebral body is squared on uoroscopy

Oblique rotation of the C-arm helps visualize the junction of the vertebra and TP

A 22G, 70/90 mm spinal needle is inserted to be positioned either on the middle third of the TP or advanced to the superolateral margin of the TP to lie over the bone at that level

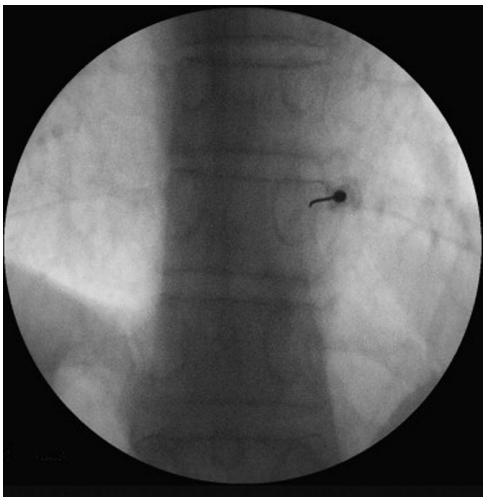
A total of 0.5–1 mL of lidocaine 1% or bupivacaine 0.25% is injected

Radiofrequency treatment of the medial branch

An RF needle (10 cm long, with a 10 mm active tip) is used instead of a spinal needle

Placement is similar to that for MBB, attempting to place the RF needle parallel to the middle third or at the superolateral margin of the TP (see Fig. 17.1.2)

For the technique, similar principles apply as with all RFs (see 15.6 Radiofrequency denervation, p. 294)



Radiofrequency needle in the superolateral position for thoracic medial branch block

Reproduced with permission from Waldman, S. (2014). *Atlas of Interventional Pain Management*, Fourth Edition. Amsterdam, Netherlands: Saunders, an imprint of Elsevier

Facet joint injection

Recognition of the facet joint is facilitated by a caudal tilt of the C-arm

The needle (22G, 70/90 mm spinal needle) insertion point may be over the pedicle, 1–2 segments caudally due to the steep angulation of the thoracic facets, advanced into the joint space

Contrast should be mixed with the LA and a small amount (0.4–0.6 mL of the mix) can be injected, avoiding larger volumes

This is not a recommended procedure due to very narrow joint space

Complications

For both MBBs and RF denervation:

- Failure of procedure to reduce pain
- Infection
- Pneumothorax

For RF denervation:

- Injury to spinal nerve roots—characterized by paraesthesiae, sensory and/or motor loss in the distribution of the spinal nerve root
- Worsening of pain for 2–4 weeks
- Dysaesthesia and allodynia of the overlying skin (for a few weeks) as a result of partial denervation of the lateral branch

Additional information

The course of the medial branch to the facet joints in the thoracic region is quite variable; therefore, some authors advise multiple targets for RF lesion extending from the superolateral margin of the TP to the lamina

The TPs are larger in the upper thoracic region. They get smaller in the lower thoracic region (T10–T12) and can be difficult to visualize. Therefore, the pedicle can be used as a landmark for needle insertion

The T12 medial branch lies at the junction of the superior articular process and the TP (similar to the lumbar medial branches)

The C-arm should be aligned in such a way that the corresponding rib lies cephalad to the TP. This will reduce the chances of pneumothorax as the needle is likely to hit the rib, rather than the pleura, if advanced too deep

RF denervation is indicated when 50% or greater improvement in pain and function (lasting for the duration of action of the LA) after MBB is obtained

Evidence

Block for symptomatic relief of facet-related pain—'level 2B'

RF ablation after positive diagnostic block (extrapolated from cervical and lumbar data)—'level 1B'

Further reading

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17.2 Intercostal nerve block

Anatomy of intercostal nerves

Anterior rami of the thoracic spinal nerves T1–T12

Enters the corresponding intercostal space lateral to the intervertebral foramen

Proximal to the angle of the rib, it travels forward in the subcostal groove between the innermost and internal intercostal muscles and inferior to intercostal vessels

Gives branches to the skin, parietal pleura, intercostal muscles (three layers of external, internal, and innermost), and serratus muscles

T7–T12 also innervate the anterior abdominal wall, parietal peritoneum, and anterior abdominal muscles, including the external oblique (EO), internal oblique (IO), transverse abdominis (TA), and rectus abdominis (RA) muscles

Indications

Analgesia for thoracotomy, intercostal drains

Rib fractures

PHN

Breast and upper abdominal surgery

Contraindications

Similar to other interventions

Patient preparation and positioning

Patient positioning: sitting, lateral, or prone position. Best position is achieved when the spine is arched and the arms extended forward in the sitting position (hugging a pillow) or hanging over the side of the bed in the prone position, as it helps to retract the scapula laterally

For abdominal surgery, T5–T12

For breast surgery, T2–T6

For thoracic incisions, 1–2 levels above and below the planned level

3–5 mL of LA at each level

Landmark technique

The inferior border of the rib to be blocked is marked at the angle of the rib

A 22G block needle is inserted cephalad until it makes contact with the rib

The needle is 'walked o ' the inferior border of the rib and advanced by 1–3 mm anteriorly

A subtle 'pop' is felt when through the fascia of the internal intercostal muscle

Correct placement will result in ipsilateral numbness of the corresponding intercostal levels

Ultrasound-guided technique

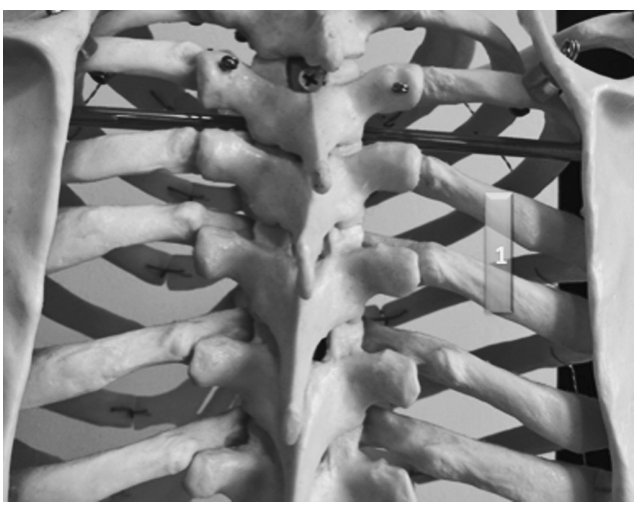
A linear, high-frequency probe in the sagittal plane

10–15 cm lateral to the spinous process (see Fig. 17.2.1)

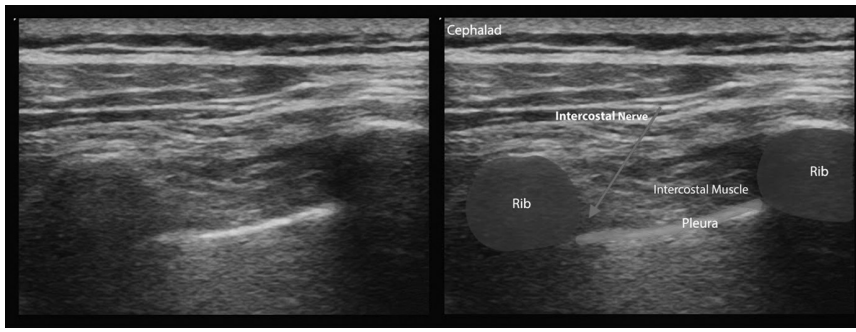
A 21–22G, 50 mm needle used, depth of around 0.5–1.5 cm

The adjacent ribs are visualized as round shadows, and the pleura as a hyperechoic line

The innermost intercostal muscle lies just above the pleura



Placement of the linear ultrasound probe



Sagittal position of the probe—sonoanatomy, in-plane approach (unlabelled and labelled)

The neurovascular bundle lies in a triangular space below the superior rib, between the internal and innermost muscles, which is the target site for injection (see Fig. 17.2.2)

In-plane or out-of-plane approach; correct placement identi ed by displacing the pleura anteriorly

Lower risk of intravascular injection and pneumothorax, and allows injection more posteriorly which also increases the chance of lateral branch block

Special points

A persistent 'comet tail' sign of the lung and pleural movement synchronized with breathing after injection excludes pneumothorax

For cancer and chronic pain, neurolytic/conventional or PRF ablation may provide longer-term bene t

Further reading

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17.3 Thoracic paravertebral block

Anatomy

The thoracic paravertebral space is a wedge-shaped space on either side of the vertebral column

Contents:

- Spinal nerves and its branches
- Sympathetic trunk
- Adipose tissue

Anatomical relations:

Anterolateral—parietal pleura, endothoracic fascia

Posteriorly—superior costotransverse ligament (SCL)

Medially—vertebral bodies and intervertebral discs, communicates with the epidural space via the intervertebral foramen

Laterally—communicates with the posterior intercostal space

Inferiorly—extends till the origin of the psoas muscle at L1

Superiorly—communicates with the cervical paravertebral space

Indications

Perioperative analgesia for thoracic, chest wall, and breast surgery

Acute pain management for rib fractures

Contraindications

Similar to other interventions

Coagulopathy

Patient preparation and positioning

Aseptic precautions

A 22G needle for single shot block, 18G or 16G for continuous block with catheter insertion

15–20mL of LA will spread 2–3 levels

Patient position—sitting, lateral decubitus with the block side up, or prone

Technique

Anatomical landmark

Needle insertion point is 2.5 cm lateral to the uppermost point of the spinous process. Advance the needle perpendicular to the skin until the needle tip hits the TP. Withdraw and redirect the needle cephalad or caudal carefully 1.5–2.0 cm past the depth where the TP is located

A change in resistance or a pop is felt as the needle traverses the SCL

Ultrasound-guided techniques

High-frequency linear US transducer probe (2–5 cm)

Transverse technique

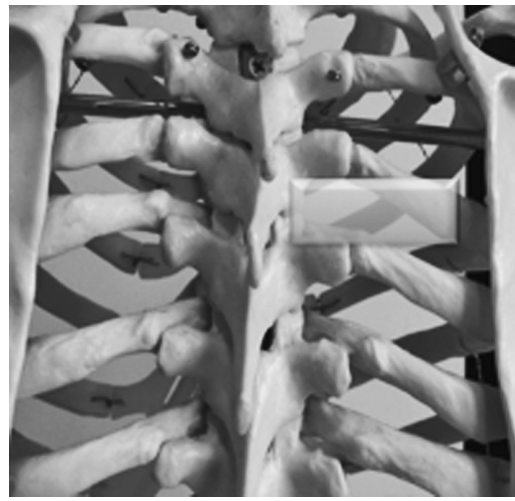
The transducer is positioned in the transverse plane at the selected level, lateral to the spinous process between the two ribs (see Fig. 17.3.1)

The thoracic paravertebral space appears as a wedge-shaped hypoechoic area bounded between two hyperechoic lines—the pleura anteriorly which moves with respiration, and the internal intercostal membrane (IIm) or the SCL posteriorly (see Fig. 17.3.2)

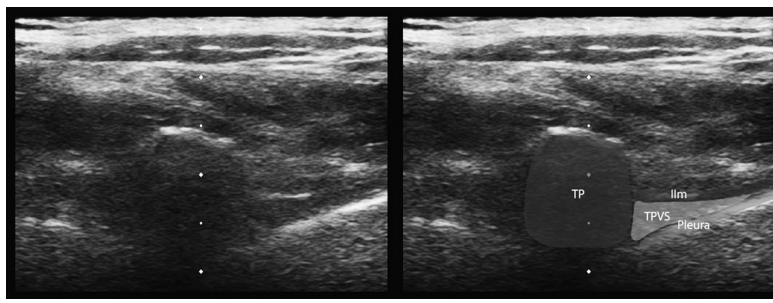
The aim is to get the needle tip through the IIm/SCL and super cial to the pleura

Out-of-plane technique

Insert the needle until it hits the TP, walk o to pierce the SCL



Transverse placement of the probe



Transverse position of the probe—sonoanatomy (unlabelled versus labelled). IIm, internal intercostal membrane (or SCL); TP, transverse process; TPVS, thoracic paravertebral space

In-plane technique

Insertion is lateral to medial, with the bevel cephalad to avoid pleural, neural, or vascular injury

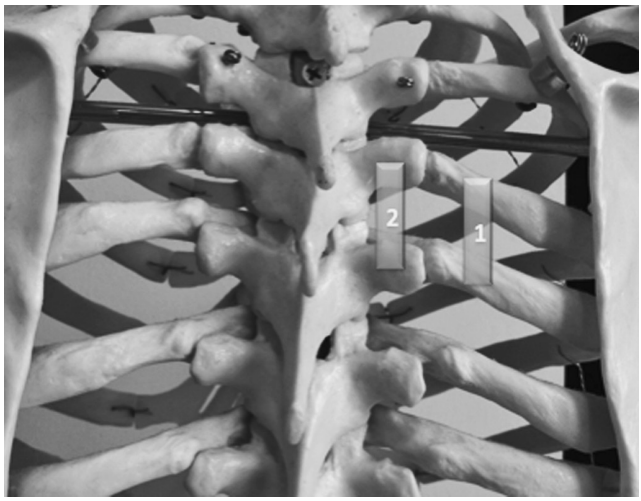
Longitudinal/parasagittal technique

The transducer is placed longitudinally 5–10 cm lateral to the spinous process where the ribs appear as rounded shadows and the parietal pleura as a hyperechoic line underneath

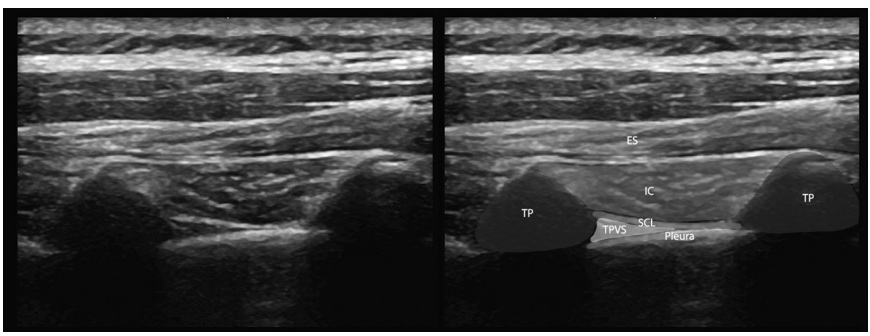
The transducer is then moved medially to less rounded and deeper shadows of the TPs (see Fig. 17.3.3)

Tilt the transducer in the sagittal axis to a slightly oblique angle, with the upper part of the transducer medial

The thoracic paravertebral space is the hypoechoic space bounded by the hyperechoic SCL and the pleura (see Fig. 17.3.4)



Longitudinal position of the probe



Longitudinal/parasagittal sonoanatomy (unlabelled versus labelled). IC, intercostal muscles; ES, erector spinae muscle; SCL, superior costotransverse ligament, TP, transverse process; TPVS, thoracic paravertebral space

Out-of-plane technique: insert the needle until it hits the TP and walk o below the IIm/SCL
In-plane technique: insert the needle cephalad or caudal and ensure the tip lies below the hyperechoic SCL. The acute angle of needle insertion can render the needle tip visualization more di cult

Complications

Pleural puncture is reported to be 5% with US in a cadaveric study, higher than with the anatomical landmark technique (1.1%)
Epidural/intrathecal spread
Bleeding
Infection
Failure

Additional information

Prone position useful in chronic pain patients as uoroscopy can be used in conjunction
The thoracic paravertebral space may be deeper in the upper thoracic regions
Loss of resistance is subtle
Real-time USS of LA injection should ideally result in anterior displacement of the pleura, considered as objective evidence of correct block placement
A lateral-to-medial approach and high-pressure injection increase the risk of epidural spread
An in-plane, parasagittal approach and an out-of-plane transverse approach are recommended for catheter placement

Further reading

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2. Luyet C, Herrmann G, Ross S, et al. Ultrasound guided placement of catheters in human cadavers. Br J Anaesth 2011;106:246–54
3. O'Riain SC, Donnell BO, Cu e T, et al. Thoracic paravertebral block using real-time ultrasound guidance. Anesth Analg 2010;110:248–51

17.4 Analgesia for rib fractures

De nition

Rib fractures are caused by blunt or penetrating forces to the chest
Flail segments occur when three or more contiguous ribs are fractured in two or more places

Incidence

10% of all patients admitted with traumatic injuries
Common after road tra c collisions and falls from height
Mortality is approximately 12%, higher in the elderly and those who develop pneumonia
Elderly patients sustain higher levels of injury from lower mechanisms
Associated with other injuries in 90% of patients

Pathophysiology

Respiratory complications are common, either due to the initial primary injury or from secondary insults
Inadequate analgesia increases the risk of developing secondary complications
Risk factors that increase mortality and morbidity (see Table 17.4.1)

Risk factors that increase mortality and morbidity

Increasing age	Flail chest
Pneumonia	Bilateral fractures
Pre-existing comorbidities	Multiple rib fractures >3
	Pulmonary contusions
	Presence of other injuries (polytrauma)

Primary respiratory complications (from the initial injury)

Contusions, haemothorax, pneumothorax, lung laceration

Secondary respiratory complications

(See Fig. 17.4.1.)

Pneumonia (up to 31% of patients)

Acute respiratory distress syndrome (ARDS)

Need for ventilatory support:

Non-invasive—high- ow nasal oxygen, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP)

Invasive—endotracheal intubation and mechanical ventilation ± tracheostomy

Risk scoring systems

Help risk-stratify and expedite the pain management of high-risk groups

Two commonly used scoring systems include the Rib Fracture Score (RFS), discussed below, and the radiologically assessed Rib Score

Rib Fracture Score

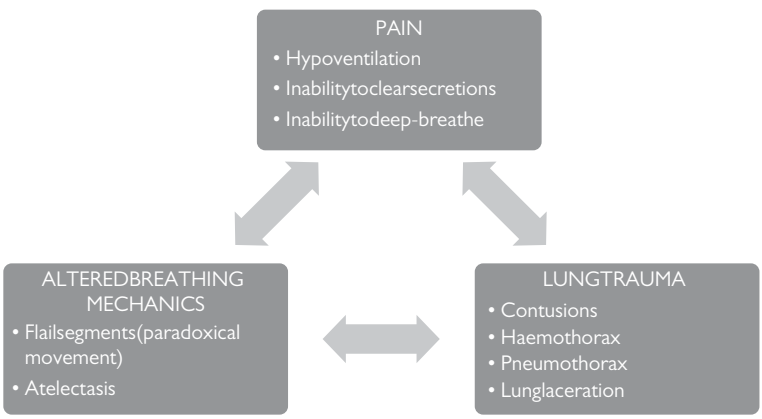
$$RFS = (breaks \times sides) + age\ factor$$

Breaks = total number of fractures to the ribs (not the number of fractured ribs)

Sides = score 1 if unilateral, score 2 if bilateral

Age factor = score 0: <50 years; score 1: 51–60 years; score 2: 61–70 years; score 3: 71–80 years; score 4: 80 years

A score of 15 suggests severe and urgent treatment should be initiated, preferably with regional analgesia



Secondary respiratory complications are in uenced by pain, altered breathing mechanics, and lung trauma

Diagnosis (history, examination/investigations, di erential diagnosis)

History

Event history, other injuries, risk of pathological rib fractures, post-CPR rib fractures

Respiratory symptoms: chest pain—worse on moving, breathing, and coughing; if delayed presentation, are features of pneumonia present?

Past medical history: respiratory disease (e.g. chronic obstructive pulmonary disease (COPD), smoking, exercise tolerance)

Examination

Full Advanced Trauma Life Support (ATLS) assessment with primary and secondary survey

Focused respiratory examination should assess for:

- Chest movement (ail segments/paradoxical chest movement)
- Tracheal deviation (tension pneumothorax)
- Chest auscultation (reduced breath sounds = pneumothorax/haemothorax; crepitations = contusion/consolidation)
- Chest percussion (hyperresonance = pneumothorax; hyporesonance = haemothorax/pleural e usion)
- Signs of respiratory distress: use of accessory muscles, rapid respiratory rate, low oxygen saturation (SpO_2) <94% (air)

Investigations

Arterial blood gas: low PaO_2 and/or high A–a gradient, raised $PaCO_2$

Chest X-ray (CXR): pneumothorax, e usion, consolidation, oedema/contusion; rib fractures may be missed

CT: gives detailed information on number, level, location, and displacement of the rib/ribs, and identi es lung pathology

Treatment

Early and e ective analgesia with multimodal approaches reduces the risk of respiratory complications and subsequent morbidity/mortality (see Table 17.4.2)

Enables compliance with physiotherapy

Surgical rib xation for those with signi cant chest injuries/ ail segments is increasing

T Multimodal analgesia

	*	
Paracetamol Non-steroidal agents (NSAIDs) Neuropathic agents (gabapentin/pregabalin) Codeine Tramadol Morphine (intermittent PO/IV bolus, PCA, continuous infusion in high dependency unit (HDU)/intensive care unit (ICU)) Ketamine infusion	Thoracic epidural Paravertebral catheter Intercostal nerve blocks Erector spinae plane catheter Serratus anterior plane catheter	Surgical rib xation

* Catheter insertion, rather than a single shot injected, is suggested.

Assessment of pain

Static (at rest) and dynamic (on movement/coughing) pain scores

Incentive spirometry as an objective assessment of analgesic adequacy

Challenges of analgesic management

Regional analgesia is favoured, but <20% of patients actually receive thoracic epidural analgesia or paravertebral analgesia due to patient, injury, and service provision factors

Patient factors

Multiple comorbidities that prevent insertion, anticoagulant medications

Injury factors

Spinal trauma and head injuries, signi cant hypotension

Service provision

Advanced level of skills required, out of hours, increased level of observation/monitoring required post-thoracic epidural/paravertebral insertion

Limitations of thoracic epidurals and paravertebral analgesia have led to a rapid rise in popularity of the novel **thoracic wall fascial plane blocks**—serratus anterior and erector spinae planes discussed below

Intercostal block (see 17.2 Intercostal nerve block, p. 318) and paravertebral block (see 17.3 Thoracic paravertebral block, p. 320) are discussed

With fascial plane blocks, larger volumes of LAs, typically 20-30 mL are needed, hence caution with LA toxicity, especially when bilateral blocks/catheters are used

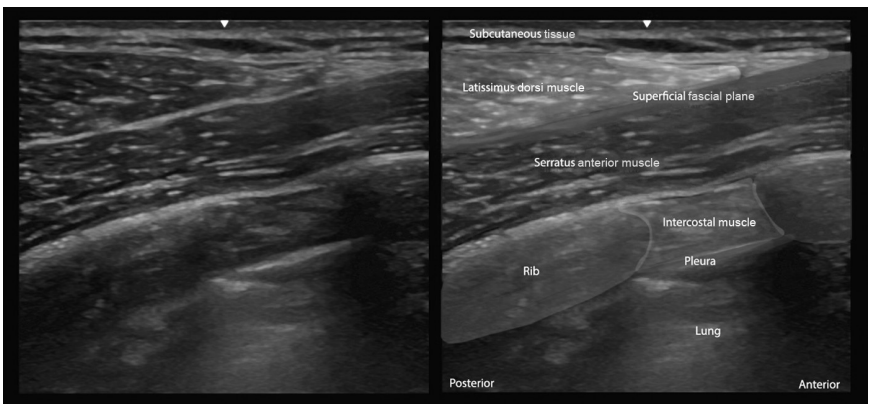
Serratus anterior plane

(See Fig. 17.4.2)

Indications

Most e ective in anterior–lateral fractures

Also e ective in breast surgery, thoracotomy, and chest drain insertion



Serratus anterior plane sonoanatomy (unlabelled versus labelled)

Mechanism of action

Anaesthesia of the lateral cutaneous nerve, with variable involvement of the long thoracic, intercostal, and thoracodorsal nerves

Covers anterior–lateral hemithorax T2–T9

Insertion

Supine or lateral positioning with US-guided in-plane needling

Transverse orientation of the probe

Anterior–posterior needle trajectory at the level of the fourth rib in mid-axillary line

Identify the super cial serratus plane between the serratus anterior and the latissimus dorsi muscles; hydro-dissect the fascial plane to enable catheter insertion

Deep injection can be performed between the rib/intercostal muscle and the serratus anterior muscle. This is a more advanced technique due to the close proximity of the intercostal vessels and pleura

Advantages

Reliable analgesia, supine position, easy to learn, no autonomic block, and block/catheters can be inserted bilaterally

Caution

Avoid the thoracodorsal vessels that run in the super cial plane

Close proximity to the pleura

Erector spinae plane

(See Fig. 17.4.3)

Indications

May be most e ective for posterior rib fractures

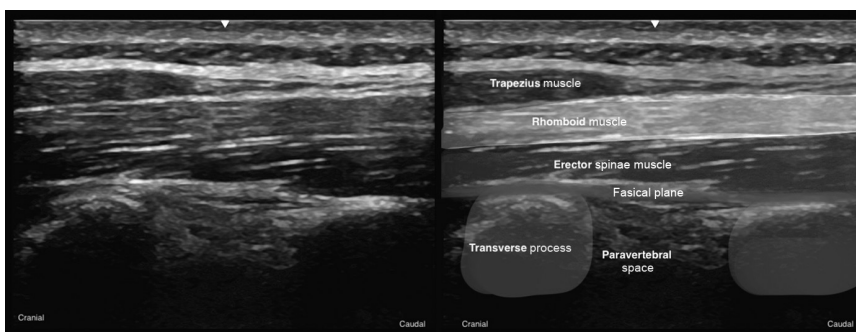
Bilateral injections/catheter insertions can be performed

Mechanism of action

Anaesthesia of the posterior (dorsal) rami of the spinal nerves

Possible anterior spread to the paravertebral space

Analgesia of the hemithorax



Erector spinae plane sonoanatomy (unlabelled versus labelled)

Insertion

- Lateral or sitting position, with US-guided in-plane needling
- Paramedian sagittal orientation of the probe and cranial–caudal needle trajectory
- Hydro-dissect the fascial plane between the Transverse Process and the erector spinae muscle

Caution

- Close proximity to the spinal nerves and pleura

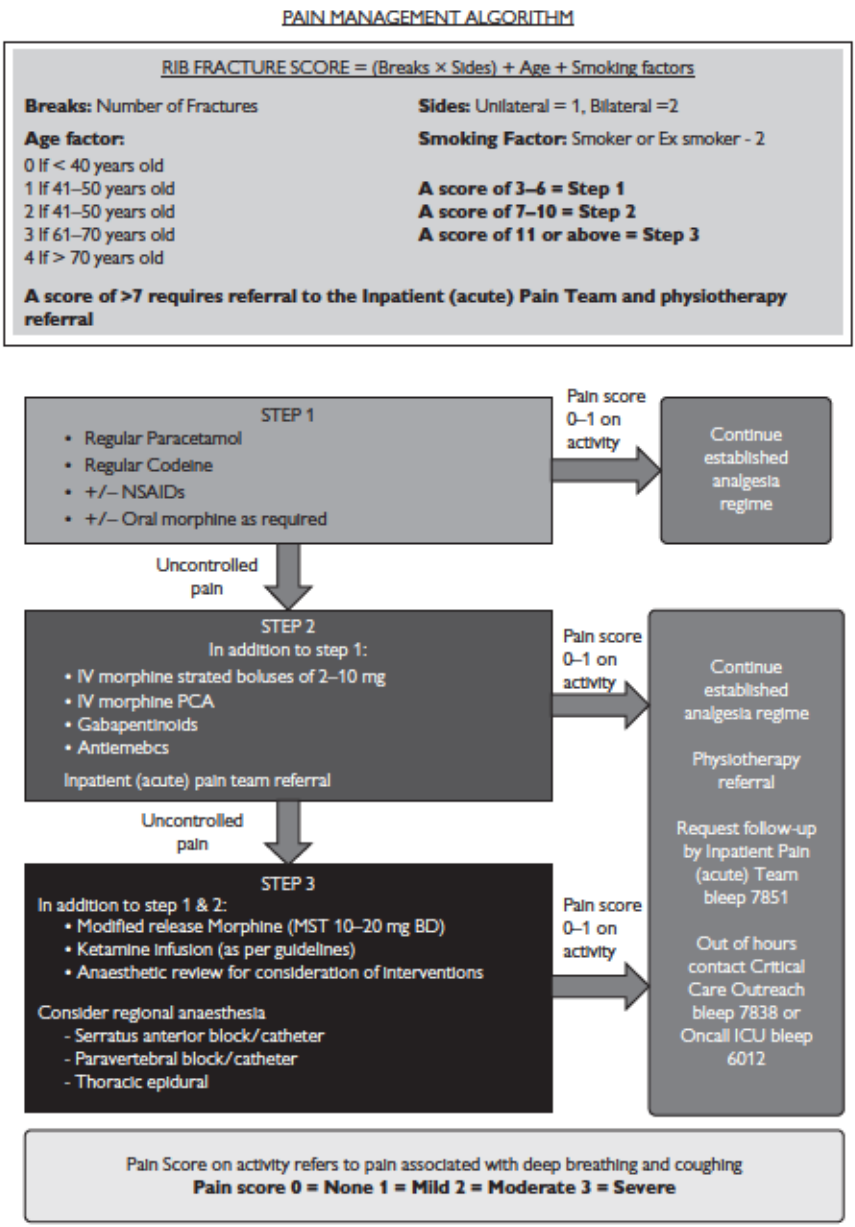


Figure 17.4.4 Sample of rib fracture pain management algorithm
Reproduced courtesy of the Dudley Group NHS Foundation Trust by SR Elaine Roe and Alifia Tameem

Further reading

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2. Chapman BC, Herbert B, Rodil M, et al. RibScore: a novel radiographic score based on fracture pattern that predicts pneumonia, respiratory failure, and tracheostomy. J Trauma Acute Care Surg 2016;80(1):95–101
3. NYSORA. Erector spinae plane block. 2019. https://app.nysora.com/courses/erector-spinae-plane-block/lessons/anatomy-20/

17.5 Abdominal wall blocks

Anatomy—overview and muscles

The anterior abdominal wall extends from the costal margins and xiphisternum superiorly to the iliac crests, inguinal ligaments and pubic crest, and the symphysis inferiorly

It comprises three muscle layers antero-laterally: EO, IO, and TA. These taper into a fascial plane medially—the rectus sheath—which encases vertically arranged rectus abdominis muscles

The fascial plane of the IO and TA converge postero-laterally with the thoracolumbar fascia. This fascia is a complex tubular structure formed by blending of aponeuroses and fascial layers. It divides into anterior, middle, and posterior layers to encase the quadratus lumborum muscle (QLM) and the erector spinae muscles

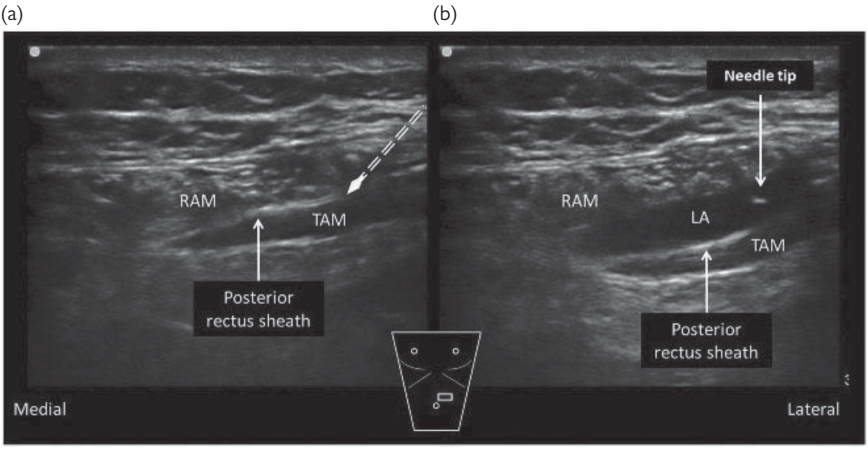
The anterior abdominal wall is innervated by the thoraco-abdominal nerves and the ilio-inguinal and ilio-hypogastric nerves

The QLM inserts on the posterior iliac crest inferiorly and the twelfth rib superiorly and the transverse processes of L1–5. It is located between the psoas major muscle (anteriorly) and the erector spinae muscle group (posteriorly)

Anatomy—innervation

The thoraco-abdominal nerves are continuations of the intercostal nerves arising from the anterior rami of T6–12. They travel infero-medially in the transverse abdominis plane (TAP). Each gives o a lateral branch, providing cutaneous sensation to the lateral abdominal wall, and an anterior branch, which pierces the rectus sheath laterally to run between the posterior rectus sheath and the posterior aspect of the RA muscle, before piercing it medially to supply the anterior abdominal wall

The ilio-inguinal and ilio-hypogastric nerves are terminal branches of the L1 nerve roots, with varying contributions from T12 and L2–3. They emerge on the lateral border of the psoas major muscle, run infero-medially, and pierce the TA muscle above the anterior superior iliac crest to run between the IO and TA muscles. The ilio-inguinal nerve supplies the superior medial part of the thigh, the base of the penis/mons pubis, and the anterior scrotum/labia majora. The ilio-hypogastric nerve supplies the skin over the inferior medial anterior abdomen



Ultrasound-guided rectus sheath block

(a) Pre-injection image. The probe is placed in a transverse orientation superior to the umbilicus to visualize the lateral aspect of the rectus abdominis muscle (RAM) and the rectus sheath. The needle is inserted deep to the lateral edge of the RAM but does not penetrate the two layers of the posterior rectus sheath

(b) Post-injection image. Injection here creates a pocket of LA between the RAM and the posterior rectus sheath

LA, local anaesthetic; TAM, transverse abdominis muscle

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Posterior rectus sheath block

(See Fig. 17.5.1.)

Indications

Para- and umbilical hernia repair

Midline laparotomy (bilateral posterior rectus sheath blocks/catheters in combination with bilateral TAP block or quadratus lumborum block (QLB) for better analgesia)

Anterior abdominal wall pain syndrome

Patient positioning

Supine

Technique

Aims to block the terminal branches of the anterior divisions of the 9th–11th intercostal nerves

Linear probe transverse and in the midline to identify the rectus muscles on either side of the linea alba and the encasing hyperechoic rectus sheath

Deposit LA between the rectus muscle and the posterior rectus sheath to separate the muscle from the sheath

The tendinous intersection of the anterior part of the rectus muscles is absent posteriorly to enable free passage of the LA

10–20 mL of LA into each side

Speci c complications

Bowel perforation

Intravascular injection (inferior epigastric vessels in close proximity)

Tips

Must block both sides as the midline receives innervation bilaterally

Can be done by surgeons at abdominal closure under direct vision who can also site LA in ltration catheters

Transverse abdominis plane block

(See Fig. 17.5.2.)

Indications

Laparotomy (bilaterally for midline incision)

Pfannenstiel incision in Caesarean section (bilaterally)

Abdominoplasty (bilaterally)

Nephrectomy

Cholecystectomy

Laparoscopic surgery

Patient positioning

Supine, with the arms placed anteriorly to expose the lateral abdomen (elevate the ipsilateral hip with sandbag, uid bag or wedge)

Technique

Aims to block thoraco-abdominal and ilio-inguinal and ilio-hypogastric nerves prior to their piercing the musculature

Transducer placed transverse in the mid-axillary line approximately midway between the costal margin and the ASIS. Moving the probe slightly posteriorly from this position often improves the view of the EO, IO, and TA muscle layers with the underlying hyperechoic peritoneum

Needle inserted in-plane anterior to posterior, and LA deposited in the plane between the IO and TA muscles

20–30 mL of LA on each side

Speci c complications

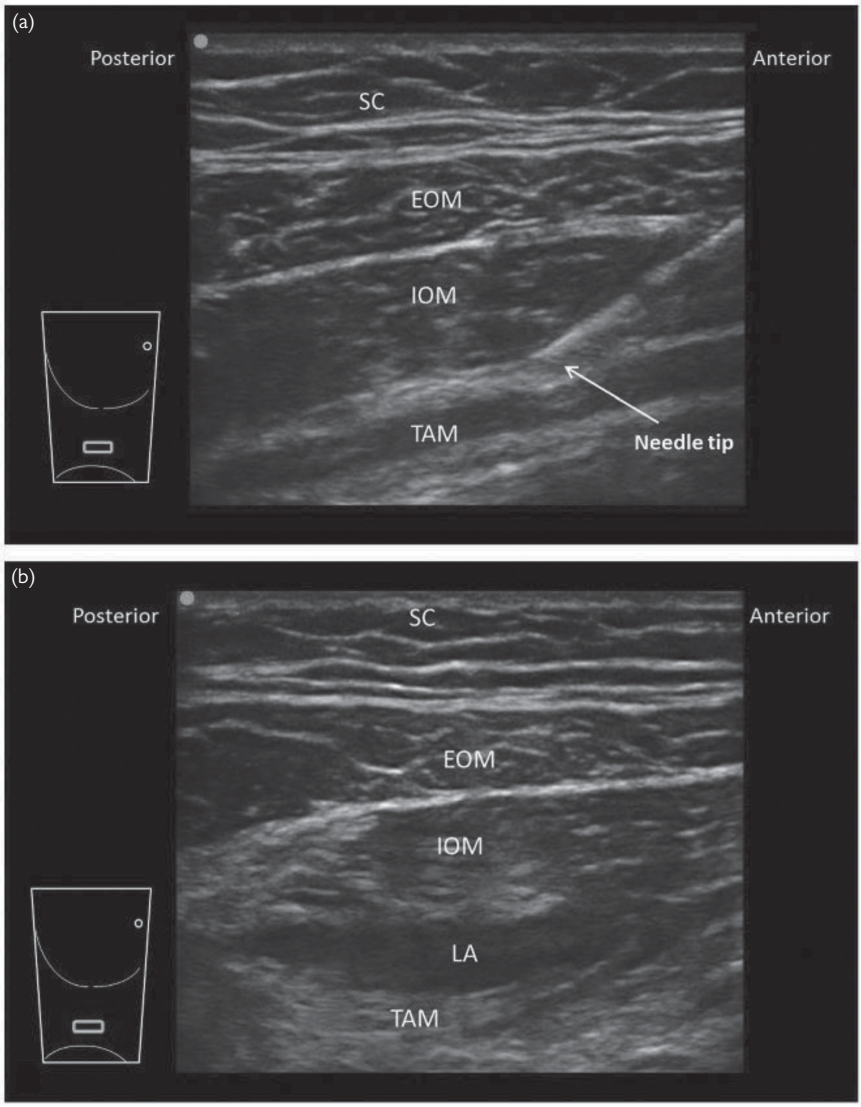
Bowel perforation

Tips

Must block both sides for midline incisions as innervation is bilateral

Volume-dependent plane block, so larger volumes of LA needed to cover multiple dermatomes (e.g. 0.6 mL/kg on each side). Therefore, saline can be used to con rm correct needle placement with hydro-dissection of the plane prior to LA administration

Unilateral subcostal TAP block immediately inferior to the costal margin can be used for upper abdominal surgery (e.g. cholecystectomy)



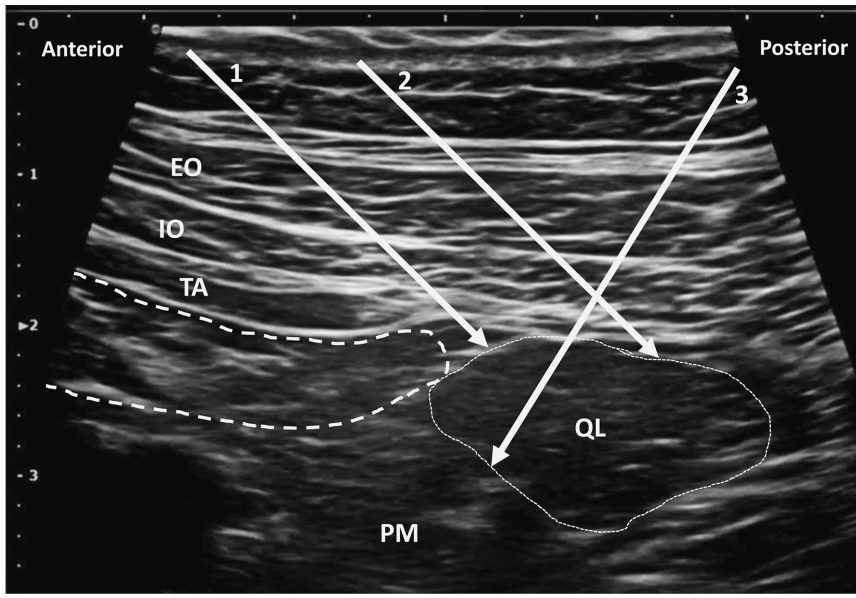
Ultrasound-guided lateral transverse abdominis plane (TAP) block

(a) Pre-injection image. The US probe is placed in a transverse orientation between the costal margin and the iliac crest in the mid-axillary line. A needle is advanced in an anterior-to-posterior direction through the muscular layers of the abdominal wall to reach the TAP between the internal oblique muscle (IOM) and the transverse abdominis muscle (TAM). The TAM has a characteristic darker hypoechoic appearance and is usually signi cantly thinner than the IOM

(b) Post-injection image. The local anaesthetic (LA) has distended the TAP, separating the IOM and the TAM

EOM, external oblique muscle; SC, subcutaneous tissue

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Three approaches to ultrasound-guided quadratus lumborum block. The ultrasound probe is placed in transverse oblique above the posterior aspect of the iliac crest

1. Anterior approach (QLB-1): the needle is advanced in a lateral-to-medial direction towards the plane between the transversalis fascia (dashed line) and the internal oblique (IO) and transverse abdominis (TA) aponeurosis

2. Lateral approach (QLB-2): the same needle trajectory is used to reach the tissue plane posterior to the quadratus lumborum (QL) muscle

3. Transmuscular or posterior approach (QLB-3): the needle is advanced in a posterior-to-anterior direction to reach the anterior surface of the QL muscle

Muscles: EO, external oblique; IO, internal oblique; PM, psoas major; TA, transverse abdominis

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Quadratus lumborum block

(See Fig. 17.5.3.)

Deposition of LA at sites lateral, posterior, and anterior to the QLM have been described as QLB-1, QLB-2, and QLB-3, respectively

Modality of analgesia incompletely understood, but spread of LA to the paravertebral or epidural space may result in visceral, as well as cutaneous, analgesia

Indications

Laparotomy
Pfannenstiel incision in Caesarean section
Abdominoplasty
Nephrectomy
Orchidopexy
Hip surgery
Lumbar vertebral surgery

Patient positioning

Supine with lateral tilt to each side, so that the side to be anaesthetized is uppermost

Another option is a pillow under the ipsilateral hip

Technique

A curved probe is placed on the postero-lateral aspect of the abdominal wall in a transverse oblique orientation, between the iliac crest and the costal margin (cranial to the iliac crest)

The EO, IO, and TA muscle layers are identi ed and followed posteriorly till the bres le o into an aponeurosis. The QLM is postero-medial to this

QLB-1: LA deposited antero-lateral to the QLM (essentially a postero-lateral TAP block)

QLB-2 block: LA deposited posterior to the QLM between the thoracolumbar fascia, which separates the QLM and the erector spinae muscles (iliocostalis)

QLB-3 block: AP transmuscular injection (through the QLM) to deposit LA anterior to the QLM

20–30 mL of LA (adjust volume if bilateral blocks are needed)

Speci c complications

Retroperitoneal organ injury

High volumes could theoretically give excessive spread within the epidural space

Further reading

1. Akerman M, Pej i N, Veli kovi I. A review of the quadratus lumborum block and ERAS. Front Med (Lausanne) 2018;5:44
2. Chin KJ, McDonnell JG, Carvalho B, et al. Essentials of our current understanding: abdominal wall blocks. Reg Anesth Pain Med 2017;42:133–83
3. Townsley P, Bedforth N, Nicholls B, et al. A Pocket Guide to Ultrasound Guided Regional Anaesthesia. 2nd edition, 2019. London: Regional Anaesthesia UK

CHAPTER 18

Lumbar and Pelvis

Sadiq Bhayani, Yehia Kamel, Yin Yee Ng, Bhavesh Raithatha, Jan Rudiger, and Thomas E. Smith

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18.1 Lumbar facet joint/medial branch blocks and radiofrequency denervation

The role of facet joint treatments

Facet joints ('zygapophyseal joints') are small synovial joints between vertebrae on the postero-lateral aspect of the spine

They allow a degree of movement of the spine, while stabilizing it against excessive movement

They are prone to degenerative/osteoarthritic changes (particularly at low lumbar and cervical levels), like other synovial joints that bear a lot of loading in our lives (knees, hips)

Pain from lumbar facet joints is felt in the lumbar paraspinal area, spreading into the buttocks and often into the posterior thighs (down to the calves)

Many pain physicians believe that facetogenic pain is worse on loading the joints (e.g. straightening the spine after exion, extension from neutral, and lateral exion with extension)

However, a limited number of studies looking at this have suggested that pain on loading of the joints is not a good discriminator, and that the main positive association is localized paraspinal muscle tenderness

Muscle tension and tenderness are seen with other drivers of axial back pain

This leads to the concept of 'back pain for investigation'

The only way to determine if facet joints are a major driver of low back pain is to treat them and see if the pain considerably diminishes

Interventional studies suggest that around 15% of cases of axial low back pain may have facet joint arthropathy as the main driver and therefore bene t from facet joint treatments

Facet joint injections

Facet joint injections with LA and steroid has been a popular treatment for chronic low back pain for decades

Although described as intra-articular injections, it is likely that in most cases, the injections are periarticular, given the difficult anatomy of degenerative joints and the small volume of the joint

The efficacy and cost-effectiveness of facet joint injections are controversial

Patient selection and operator factors are likely to play important roles in determining outcomes

Past studies reported by interventionalists reported mildly positive outcomes, but in recent years, evidence and opinion have shifted towards the conclusion that facet joint injections have limited efficacy and are not cost-effective in larger populations

Repeated facet joint injections are no longer recommended for low back pain in the UK

However, there are some patients who show remarkable and prolonged benefit from traditional facet joint injections, and it may be reasonable to continue to offer these injections to a select group

Facet joint medial branch blocks and rhizolysis leading to facet joint denervation

An alternative to injecting the facet joint or periarticularly is to block or destroy (lesion) the nerves that supply it

Each facet joint is supplied by two small branches of the posterior medial branch nerves (from the level above and below the facet joint)

At the lumbar levels, these nerves run in relatively reliable positions as they approach the joint (see Fig. 18.1.1)

Using X-ray or US guidance, these nerves can be blocked with small volumes of LA (0.3–0.5 mL) to assess the role of the facet joints in contributing to the pain

This is known as a **diagnostic block** procedure. The LA effect lasts only for hours, so one is looking for short-lived, but significant pain relief (>50%) to occur

Patients are required to record their pain and function before and after the blocks

If a short-lived, but significant reduction in pain occurs, then the patients can be offered RF rhizolysis (burning of the nerves)

This is a procedure using an RF generator designed for that purpose and needles with special tips and an electrode inside the needle that can be heated to a controlled temperature while delivering a controlled amount of energy

This creates small burns several millimetres long and wide that 'lesion' the nerves

This is a day case procedure requires X-ray imaging and operator expertise

The burning also damages adjacent tissue; therefore, the back tends to be painful for a week or two afterwards

However, once the post procedural acute pain settles down, benefit from the resulting 'denervation' of the facet joints is expected

The benefit should last for 9 months or longer—but the destroyed nerves grow back over time

Facet joint MBBs for pain investigation and, if positive, RF rhizolysis to produce facet joint denervation are supported by current evidence and latest UK guidelines

In April 2020, consensus guidelines were published on interventions for lumbar facet joint pain, with the following recommendations (evidence grades 'A' and 'B' indicate to offer/provide service, 'C' to offer/provide service for some patients, and 'D' to discourage use of service; and 'I' means if offered, patients need to understand the risk–benefit balance):

History and examination did not predict reliably the response to facet joint blocks—paraspinal tenderness had a weak positive correlation; pain pattern and imaging can be useful (C)

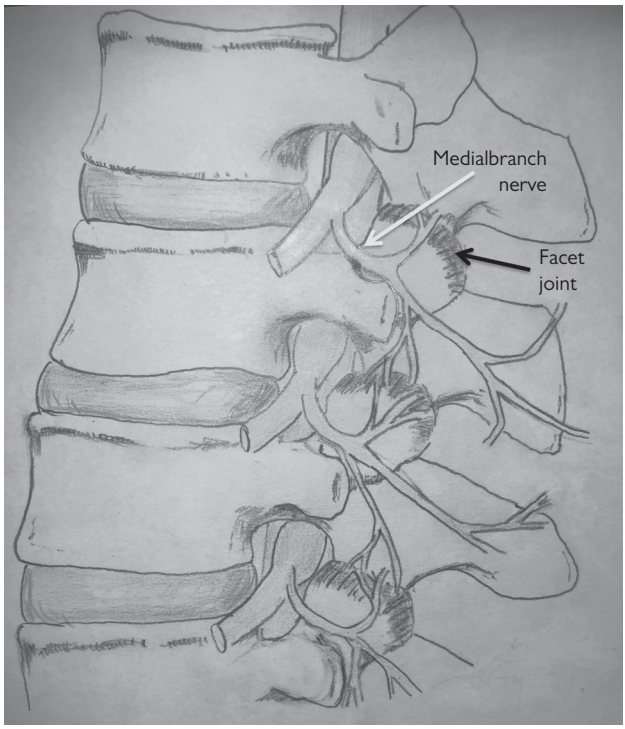


Illustration of the lumbar spine with facet joints and medial branch nerve

Investigations: weak to moderate evidence for MRI, CT, scintigraphy, and single-photon emission computed tomography (SPECT) before intra-articular blocks (D) and before MBBs (C)

A 3-month trial of di erent **conservative treatments** can be o ered to some patients (C)

CT and uoroscopy (US can be considered) are recommended for MBBs or intra-articular facet joint injections (C, D)

Intra-articular blocks seem of higher diagnostic value than **MBBs** (C)

MBBs and intra-articular injections are better than saline for diagnostic blocks (B)

MBBs are the prognostic injection of choice prior to RF; intra-articular injections can be used in some patients (C)

Sedation is not routinely recommended (B)

The ideal volume for MBBs is 0.5 mL of LA, and <1.5 mL for intra-articular injections (C)

Therapeutic use of MBBs and intra-articular injections are only recommended if they produce prolonged pain relief and if RF ablation is contraindicated (D)

More than 50% pain relief is regarded as positive for RF; secondary outcomes should be considered (e.g. activity levels) (B)

For **prognostic blocks**, a single block is recommended, but multiple blocks (e.g. two) may improve the outcome (C)

RF: larger lesions can improve the outcome (e.g. larger electrode, higher temperatures, longer duration, electrode orientation, uid modulation) (C, I)

There is evidence that near-parallel orientation of the electrode is bene cial (B)

Sensory stimulation is recommended for single lesion (C)

Motor stimulation is recommended for safety and e ectiveness (B)

Complications:

IV uptake is of low validity of MBBs (C)

Anticoagulation can be continued for facet blocks and RF ablation (B)

There is limited evidence for the use of steroids after RF ablation (C)

Multiple views and sensorimotor testing are recommended to lower the risk of nerve root injury (B)

There is the possibility of paraspinal muscle degeneration and disc degeneration; therefore, physiotherapy needs to be considered prior to RF denervation (C)

Consider interference with implanted electrical devices (turning o neurostimulators, using bipolar RF, grounding pads away from cardiac devices, avoiding excessive sedation) (C)

Avoid equipment malfunction or burns (check equipment, dry clean and shave legs for good contact) (B)

Lower success rate after spine surgery (avoid contact with metalwork, multiple views to check needle position) (C)

Di erent selection and performance criteria can in uence the outcome (A)

Repeat RF ablation in patients with >3 or, better, >6 months of pain relief (up to twice per year); the success rate of RF ablation decreases (but pain relief remains above 50%) (B)

Repeat prognostic blocks are not needed if the pain pattern remains over time (C)

Further reading

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18.2 Sacroiliac joint block and radiofrequency denervation

Anatomy

Largest axial joint in the human body with an average surface area of 17.5 cm^2

A diarthrodial joint between the sacrum and the ilium where only the anterior part is a true synovial joint

The posterior part is a syndesmosis consisting of both the gluteus medius and minimus muscles, the piriformis muscle, and the sacroiliac ligaments

Both SIJs move together as a single unit

Contains hyaline cartilage on the sacral side and brocartilage on the iliac side

SIJ stability depends on both the bony structure and a combination of intrinsic and extrinsic strong ligaments (anterior and posterior SIJ ligament, interosseous SIJ ligament, sacrospinous ligament, sacrotuberous ligaments). These ligaments serve to limit movement in all planes

Degenerative changes a ecting the joint start at puberty and progress throughout life, restricting motion

Several muscles attach to the SIJ: gluteus maximus and medius, psoas, latissimus dorsi, multi dus, piriformis, biceps femoris, obliquus, transversus abdominis

Nerve supply:

- Anterior part: variably by L2–S2, L4–S2, and L5–S2
- Posterior part: variable from lateral branches of L4–S4 posterior primary rami

Indications

Intra-articular causes: spondyloarthropathy, OA, malignancies, infections, idiopathic, metabolic

Extra-articular causes: ligaments, myofascial, fractures, enthesopathy

Contraindications

Absolute: patient refusal, infection (systemic or local), coagulopathy, profound psychopathology

Relative: anatomic abnormalities or previous surgeries in the vicinity of the joint

Patient preparation, equipment, and positioning

In patients with failed back surgery syndrome, a recent MRI scan is a must

Explanation of the technique and complications, including failure, infection, numbness in the area, and bowel and bladder dysfunction

A 22G, 88–100 mm needle for the block. Alternatively, for RF procedures, use a 10 cm RF needle with a 5–10 mm active tip. Either needle could have a straight or curved tip

Prone and full asepsis; place a pillow underneath the iliac crests to neutralize lumbar lordosis

Intra-articular technique

Having positioned the C-arm in a PA view, angle it to the contralateral oblique side to separate the anterior and the posterior SIJ lines, so as to view the widest gap at the most inferior aspect of the joint. The medial line corresponds to the posterior SIJ line. Tilting the C-arm in a craniocaudal direction may help visualization

After skin in ltration of the lower part of the joint with lidocaine 1%, introduce the 22G needle until the tip is felt within the joint

Con rm the position with 0.5–1 mL of contrast. Ideally it should spread within the perimeter of the joint, covering the dorsal and ventral joint lines

Inject 5 mL of LA ± steroid

Radiofrequency lesioning techniques

Lateral branch sensory-guided radiofrequency neurotomy

Position as above, aiming to visualize the sacral foramina

Aim to target the posterior primary ramus of L5 and the lateral branches of the posterior primary rami of S1–S3

Standard RF needles

Con rm by sensory stimulation at 50 Hz reproducing concordant pain at <0.5 V. Exclude contact with radicular motor nerves and those controlling sphincters by motor stimulation at 2 Hz between 1.5 V and 2 V (more than twice the voltage needed to achieve sensory stimulation)

Check the lateral view to exclude needle positions deeper than the sacral cortex

RF lesion at 85°C for 60 seconds. Some clinicians perform 2–3 lesions per sacral level, 1 cm apart

Bipolar radiofrequency palisade technique

Position and prepare as above

Six RF needles with a 10 mm active tip

Using a postero-anterior view, identify and mark a line between the lateral side of the sacral neural foramina and the SIJ

In the lateral C-arm view, insert the cannulae perpendicular onto the sacrum along the marked line extending from higher than S1 and ending inferior to S3

The cannulae should be placed parallel to each other and almost 10mm apart

Perform motor stimulation between each two adjacent cannulae by 'leap-frogging'. Forgo sensory stimulation

Perform bipolar RF lesions also between adjacent needles by 'leap-frogging' at 85°C for 60 seconds

Simplicity™ radiofrequency technique

Simplicity™ is a curved multi-electrode probe

Position and prepare as above

A single entry point at 1cm lateral and inferior to the S4 foramen in the lateral inferior sacral border

Using a 25G, 10 cm needle, in ltrate the skin and the path to be taken by the Simplicity™ probe with lidocaine 1%, avoiding intraforaminal injection

From the entry point, establish contact with the periosteum

Advance cranially and laterally, lateral to the foramina and medial to the joint, until it reaches the sacral ala

Adjust the position to ensure the three independent electrodes are well positioned to lesion the S1–S4 lateral branches

The L5 posterior ramus will have to be lesioned as usual

SInergy™ cooled radiofrequency technique

Allows performance of larger lesions with a volume equal to 8–10 thermal RF lesions.

More predictable ablation that can overcome the anatomical variability of the S1–S3 lateral branches

The target is the L5 dorsal ramus and the lateral branches of S1–S3

A special introducer with a stylet is used to be replaced by the RF probe which then extends 4 mm beyond the tip

The needles should be placed 8–10 mm from the lateral foraminal edge

The active tip is cooled to 60°C by a water pump

A total of nine lesions are performed: one at L5, three at S1 and S2, and two at S3

Pulsed radiofrequency technique

Targets are: L4 medial branch, L5 dorsal ramus, and S1–2 lateral branches

Two pulsed lesions at 39–42°C at 45 V for 120 seconds

Evidence for interventions for sacroiliac joint pain

Intra-articular steroids and LA	1 B+
Thermal RF of lateral and dorsal rami	2 C+
PRF of lateral and dorsal rami	2 C+
Cooled RF	2 B+

Complications

Haematoma, nerve damage, sciatic nerve trauma (very rare), temporary flare-up of pain secondary to neuritis, weakness in cases of extra-articular extravasation, vascular particulate embolism, transient perineal numbness, allergic reaction to drugs used

Summary of evidence

(See Table 18.2.1.)

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18.3 Coccygeal block and ganglion impar block

Anatomy of coccygeal nerve

Exits the sacral canal from the sacral hiatus at the level of the sacral cornua

Innervates the coccyx and the skin surrounding the coccyx

Anatomy of ganglion impar

Most caudal ganglion of the sympathetic trunk located at the sacro-coccygeal junction

Lies midline in the retroperitoneal space, anterior to the coccyx

Consists of grey rami communicantes, with grey nerve fibres connecting with the spinal nerves. Lacks white nerve fibres which connect the spinal nerves to the sympathetic ganglia at the thoracolumbar area

Receives visceral afferent from the anus, distal rectum, perineum, vulva, distal third of the vagina, and distal urethra

Indications

Coccygeal nerve block: coccygodynia (see 23.12 Coccygodynia, p. 473)

Ganglion impar block: visceral or sympathetically mediated pain in the perineum, pelvis, genitalia, or coccygodynia

Speci c contraindications

Distorted anatomy

Patient positioning

Prone position, pillows under the hips and ankles

Technique

Coccygeal nerve block

Determine the sacro-coccygeal interspace in AP view

LA in ltration to be injected for needle trajectory to the mid coccyx using a 23G needle

Insert a 21-23G needle, and advance using a perpendicular needle trajectory technique

Rotate the C-arm to obtain a lateral view

Injection of LA/steroid mix should be performed when the needle approaches the coccyx

The needle should then be walked upwards to the sacro-coccygeal interspace, injecting LA/steroid at this point

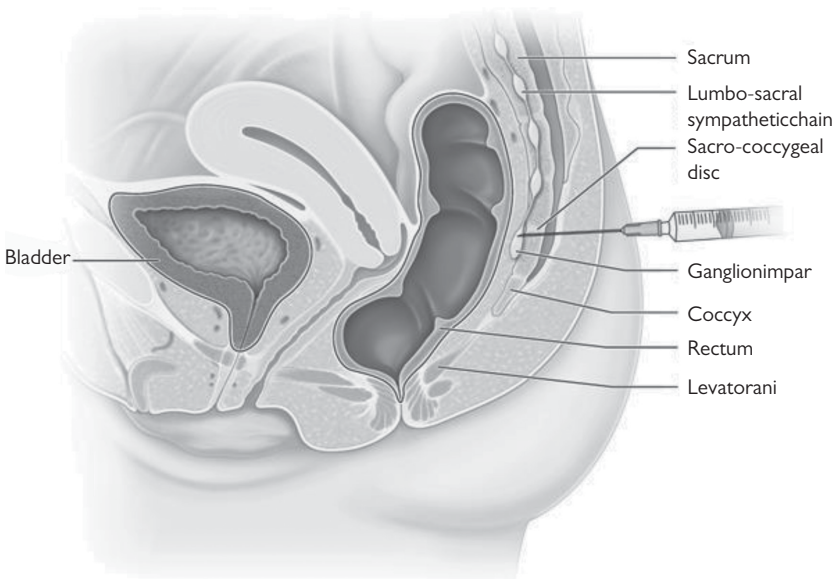
The needle should be walked down to the distal coccyx, injecting LA/steroid at this point

Contrast should be used before injecting to prevent the risk of any vascular spread and con rm correct positioning

Ganglion impar block

Determine the sacro-coccygeal interspace in AP view (see Fig. 18.3.1)

LA in ltration to be injected for needle trajectory to the sacro-coccygeal interspace using a 23G needle



Ganglion impar block.

Reproduced with permission from Diwan, S., and Staats, P., S. (2015). *Atlas of Pain Medicine Procedures*. New York city, USA: McGraw-Hill Education

Insert the 21-23G needle, and advance using a perpendicular needle trajectory technique to the C-arm

Rotate the C-arm to obtain a lateral view, advancing the needle to the anterior aspect of the coccyx

Inject contrast to determine the position and any vascular spread. Contrast should demonstrate an inferior and superior spread, with a teardrop appearance on uoroscopy

Injection of LA/steroids once con rmed

Complications

Common: sympathetic nerve block causing diarrhoea, hypotension

Rare: infection, bleeding, nerve injury, LA toxicity, visceral injury (rectum)

Special points

Remaining in midline to the coccyx (in AP view) and ensuring the needle trajectory is not too anterior to the coccyx to avoid rectal injury

Can also be performed under US guidance, with use of uoroscopy to con rm contrast spread and avoid vascular injection

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18.4 Caudal epidural

Anatomy

The dural sac usually terminates in babies at S4 and rises to S2 in adults

The epidural space extends beyond and is accessible via the sacral hiatus located between the two sacral cornua (unfused S5 vertebral lamina) and the sacro-coccygeal ligament, with extension of the ligamentum avum overlying it

Sacral canal contents (average 30–35 mL): lum terminale, termination of the dural sac, Batson's venous plexus, epidural fat, sacral and coccygeal nerves

Indications

Acute pain in paediatric surgery below the umbilicus (general surgery, urology, orthopaedics)

Persistent low back pain:

- Subacute or chronic lumbo-sacral radiculopathy—can provide short-term improvement in pain and disability in patients not responding to conservative or non-surgical management for continued radicular pain
- Lumbo-sacral spinal stenosis—evidence is limited (careful injection and monitoring of patient)
- Non-speci c low back pain—evidence does not show a strong bene t in pain, disability, or reduction of patients undergoing spinal surgery

Contraindications

Absolute: patient refusal, bleeding diathesis, infection, allergy

Relative: spina bi da/anatomical variation

Patient preparation and positioning

Prone/lateral decubitus

Technique

Landmark with uoroscopy/US guidance improves accuracy

Asepsis, thorough skin disinfection

Use a line between the posterior superior iliac spines (PSIS) as the base of an equilateral triangle and approximate the apex caudally as the sacral hiatus

In ltrate the skin entry point with LA

Insert a 21–22G, short-bevel needle/20–22G cannula at an angle of approximately 45° to the sacrum, and advance the needle cephalad. If bone is contacted, redirect the needle to reduce the insertion angle relative to the skin

Following loss of resistance, advance the needle 2 mm/advance the cannula over the needle, and remove the needle

Allow time for CSF/blood ow out in the event of intradural/intravascular placement

Aspirate gently as the vessel wall can collapse, producing a false negative

If uoroscopy is used, inject radio-opaque contrast (1 mL) to demonstrate spread in the canal

Inject drug mixture, and observe/palpate for midline swelling (super cial injection)

Drugs used:

LAs: 1–2% lidocaine, 0.1–0.5% bupivacaine, 0.2–1% ropivacaine

Adjuvants (extend block duration): clonidine 1 mcg/kg, preservative-free opioids (diamorphine 30 mcg/kg, morphine 50 mcg/kg), steroids (e.g. 40 mg triamcinolone)

Adult dose:

20–25 mL of 0.125–0.5% bupivacaine

Use low concentrations of LA if want to avoid a motor block

Paediatric dose (Armitage formula with 0.25% bupivacaine):

Sacral–lumbar block: 0.5 mL/kg

Upper abdominal block: 1 mL/kg

Mid-thoracic block: 1.25 mL/kg

Duration 4–8 hours

Complications

General

Failure, bleeding, bruising, infection, nerve injury, medication allergy

Speci c

Super cial/periosteal injection, lower limb motor block (rarer with lower LA concentration), temporary/permanent worse pain, autonomic dysfunction (higher blocks), post-dural puncture headache, intravascular injection

Special points

Di erences between adult and paediatric caudal epidurals

Unpredictable upper abdominal and thoracic spread in adults

Approximately 5% variability and di culty in locating the sacral hiatus (complete absence to the bi da of the sacrum) in adults

Higher paediatric block as less dense and less tightly packed epidural fat, better LA spread with predictable relationship between age, volume of injection, and height of block in pre-adolescent children

Easier, higher success rate (approximately 95%) in paediatrics

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18.5 Piriformis injection

Anatomy

The piriformis muscle originates from the anterior surface of the S2–S4 sacral vertebrae, the capsule of the SIJ, the anterior sacrospinous, and the sacrotuberous ligament

It is the only muscle coming out of the greater sciatic foramen and after exiting the foramen, it becomes tendinous and inserts into the upper border of the greater trochanter

Neurovascular structures that enter the buttock area from the pelvis pass either superior or inferior to the piriformis

The inferior gluteal artery and nerve, the pudendal artery and nerve, and the sciatic nerve pass below the piriformis muscle although there is signi cant anatomical variability

The undivided sciatic nerve most commonly passes below the piriformis muscle. The second most common arrangement is the divided nerve passing through and below the muscle

Indications

Piriformis syndrome (see 23.13 Piriformis syndrome, p. 475)

Contracture or spasms of the piriformis muscle secondary to trauma/surgery

Overuse and hypertrophy of the piriformis muscle

Abnormal course of the sciatic nerve through the piriformis muscle can lead to sciatic nerve irritation, giving rise to radicular symptoms in the leg

Contraindications

Patient refusal

Allergy to LA, steroids, and botulinum toxin

Relative contraindications: coagulopathy, oral anticoagulants

Patient preparation and positioning

Patient position: prone

Full monitoring and consent

Equipment: curvilinear, low-frequency (2–5 Hz) US probe

Technique

(See Fig. 18.5.1.)

Scanning is performed in the transverse plane, with the probe placed caudad to the PSIS. The ilium is visualized as a hyperechoic line running across the scan image from medial to lateral

The probe is then moved caudally to the sciatic notch. When the probe is on the sciatic notch, the hyperechoic line of the ileum is broken into two halves and the shadow of bone (ischium) comes into view in the lateral part of the scan image

At this level, two layers of muscles—the gluteus maximus muscle dorsally and the piriformis ventrally—will be visualized

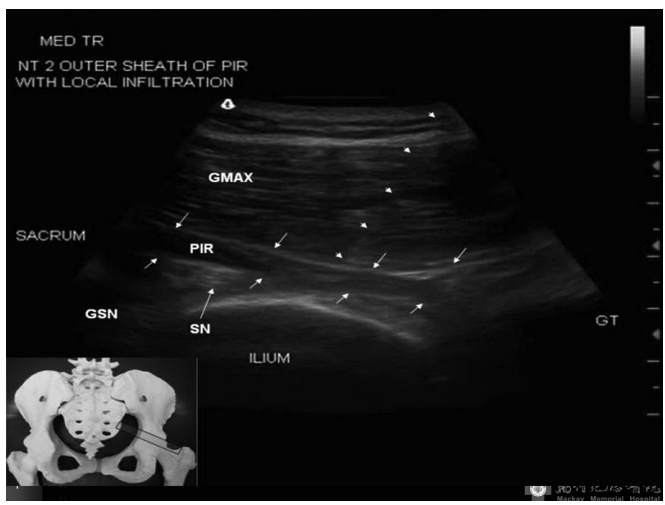
Rotating the hip internally and externally, with the knee exed, will make the piriformis muscle glide underneath the gluteus maximus muscle

The origin and insertion of the piriformis muscle can be traced by moving the probe in a medial-to-lateral position

A 100 mm, short-bevel nerve block needle is usually inserted from medial to lateral, using an in-plane technique

A total of 2–4 mL of LA and steroid is injected. BTX-A (50–100 Allergan units) with saline can also be used after successful diagnostic block.

Complications



Anatomy of the piriformis muscle (arrows) and needle path (arrowheads). GMAX, gluteus maximus muscle; GSN, greater sciatic notch; GT, greater trochanter; PIR, piriformis muscle; SN, sciatic nerve

Reproduced courtesy of Dr Sean Lin

Failure

Sciatic nerve block—motor weakness

Sciatic nerve injury

Additional information

Given the anatomical variation of the sciatic nerve in relation to the piriformis muscle, use of a nerve stimulator and a short-acting LA (lidocaine) is recommended

Hydro-dissection using 0.9% saline will help to con rm the needle tip position in the muscle

Other external hip rotators (obturator externus, superior and inferior gemellus muscle) forming the tricipital tendons below the ischial spine may be mistaken for the piriformis. It is important to scan from the ileum and locate the sciatic notch to avoid this misinterpretation

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CHAPTER 19

Autonomic Nervous System

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19.1 Anatomy of the sympathetic and parasympathetic nervous systems

Introduction

The autonomic nervous system (ANS) is divided into two antagonistic systems—the sympathetic and the parasympathetic systems, which are separate entities. These provide innervation to visceral organs, the circulatory system, and their smooth muscle cells. Myo broblasts and myoepithelial cells require a speci c system of motor neurons as part of the ANS

Most activities of the ANS are involuntary—the ANS is distinct from the somatic motor system that innervates skeletal muscles which are subject to voluntary control.

ANS activity is usually regulated by the re ex arc with an a erent limb (visceral and/or somatic) and an e erent limb (autonomic and/or somatic). A erent bres convey stimuli from the skin (nociceptive) and from sensors in organs (noci-, mechano-, and chemosensors) such as the lungs, GI tract, bladder, vascular system, and genitals. E erent bres convey information to smooth muscle cells in organs such as the eye, lung, heart, blood vessels, digestive tract, bladder, glands, and skin.

The regulation of visceral functions depends on the ANS, including eye sight, salivation, HR, BP, respiratory functions, digestion, urination, defecation, reproduction, and sweating

Most organs are innervated by sympathetic and parasympathetic nerve bres. The organ's response to the sympathetic and parasympathetic systems can be either antagonistic (e.g. in the heart) or complementary (e.g. sex organs).

Simple re exes can take place within an organ, while complex re exes are controlled by the CNS, primarily in the spinal cord

Anatomy of the sympathetic nervous system (thoracolumbar origin)

Two types of neurons: preganglionic (cholinergic) and post-ganglionic (adrenergic)

Preganglionic cells originate from the lateral grey column of the spinal cord from segments T1 to L2/3

They project mostly to a chain of paravertebral ganglia—the sympathetic trunk—where they synapse with post-ganglionic neurons

Post-ganglionic neurons extend long axons to their visceral target organs

The paravertebral ganglia are interconnected by white and grey matter (commissura alba and commissura grisea) to form a chain that extends up to the cervical and down to the sacro-coccygeal segments

Usually, there are three cervical, 11 thoracic, four lumbar, four sacral, and one coccygeal sympathetic ganglia. They do not exactly match the vertebral segments due to the fact that some ganglia fused during development

Some sympathetic nerves bypass the paravertebral ganglia to innervate the prevertebral ganglia in close proximity to their targets (e.g. thoracic splanchnic nerves)

There is no lateral column in the cervical portion of the spinal cord, and consequently no part of the ANS. Cervical sympathetic ganglia and their projections to the head therefore receive their innervation from thoracic segments

Lower lumbar, sacral, and coccygeal sympathetic ganglia receive their innervation from the lateral columns of the lower thoracic and first lumbar segments. They connect to thoracic, abdominal, and pelvic plexuses

Cervical ganglia innervate smooth muscles of the eye, cranial blood vessels, oral mucosa, and salivary glands (lacrimal, submaxillary, sublingual, and parotid)

Upper thoracic ganglia (T1–4) innervate the heart, larynx, trachea, and bronchi

The coeliac ganglion (via the greater and lesser splanchnic nerves, T5/6 to T11/12) innervates the stomach, abdominal blood vessels, liver and bile duct, pancreas, spleen, adrenal gland, and small and large intestines (superior mesenteric ganglion)

The inferior mesenteric ganglion (T12/L1 to L2/3) innervates the rectum, kidneys, bladder, uterus, gonads, and external genitalia

The ganglion impar innervates the coccygeal ganglia

Anatomy of the parasympathetic nervous system (cranio-sacral origin)

Preganglionic neurons (cholinergic) of the parasympathetic nervous system originate from the nuclei of CN III, VII, IX, and X in the brainstem and the lateral grey horn in the lower lumbar and sacral portions of the spinal cord

Parasympathetic portions of cranial nerves terminate in specific cephalic ganglia. Their post-ganglionic neurons are cholinergic and innervate glands or smooth muscles

The vagal nerve (X) provides parasympathetic innervation to countless visceral (intramural) ganglia in the neck, thorax, and abdomen, ranging caudally as far as the left flexure of the transverse colon. Post-ganglionic neurons extend short projections

The lumbo-sacral outflow innervates the visceral ganglia through pelvic splanchnic nerves (S2–4)

CN III innervates the eyes (via the ciliary ganglion)

CN VII and IX innervate the mucosa of the nose and mouth, and the lacrimal, submaxillary, and parotid glands (pterygopalatine and otic ganglion)

CN X (vagal nerve) innervates the heart, larynx, trachea, bronchi, oesophagus, stomach, abdominal vessels, liver, bile duct, pancreas, and small and large intestines (smooth musculature: Auerbach and Meissner plexuses in the gut, intestinal glands)

Lower lumbar levels to S5 innervate the large intestine, rectum, kidneys, bladder, gonads, and external genitalia

Physiology and neurotransmitters

The **sympathetic nervous system** facilitates the body's response to stressors by utilizing energy and enhancing metabolic activity (ght-or- ight response). Preganglionic neurons release ACh which activates post-ganglionic cells via speci c receptors. Post-ganglionic neurons release noradrenaline which acts through adrenergic receptors

The **parasympathetic nervous system** is dedicated to energy conservation and regeneration, e.g. through digestion, decrease in BP, and/or decrease in HR. Both preganglionic and post-ganglionic neurons of the parasympathetic nervous system are cholinergic, hence utilize ACh for activation of their targets

Clinical signi cance

The di erent neurotransmitters involved in the control of the ANS allow for pharmacological therapy with either sympatholytic or sympathomimetic e ects. Pharmacotherapy of hypertension utilizes these e ects

Autonomic neuropathy as a complication of diabetes may be caused by damage to autonomic nerves, resulting in the patient´s inability to control HR, BP, or blood sugar levels

In heart failure, the sympathetic nervous system increases its activity, leading to increased force of muscular contractions that, in turn, increases the stroke volume, as well as peripheral vasoconstriction. These e ects accelerate disease progression

Sympathicotonia is a stimulated condition of the sympathetic nervous system, marked by vascular spasm and elevated BP

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19.2 Stellate ganglion block

Anatomy

Formed by fusion of inferior cervical and rst thoracic ganglia at level of C7–T1

Loose anatomical relationship with the lower sympathetic chain

Lies anteriorly or immediately lateral to the longus colli muscle, the C7 and T8 nerve roots, and the C7 body at the base of the C7 transverse process

Lies postero-lateral to the carotid artery, posterior to the vertebral artery, and cranial to the dome of the pleura

Indications

Neuropathic pain, including acute herpes zoster, PHN, and phantom limb pain

CRPS—upper limb

Ischaemic conditions, including vascular insu ciency, Raynaud's disease, reimplantation surgery, upper limb arterial embolism, and treatment of accidental intra-arterial drug injection with thiopentone
Chronic refractory angina
Sympathetically mediated cancer pain of the head and neck
Cluster headache
Di erentiation of sympathetically maintained pain syndromes of the head and upper extremity versus sympathetically independent ones
PTSD
Refractory ventricular tachycardia

Contraindications

Patient refusal
Localized or systemic infection
Coagulopathy or thrombocytopenia
Distorted or complicated anatomy
Contralateral phrenic nerve palsy or advanced respiratory disease
Previous lower anterior cervical surgery

Patient preparation and positioning

General principles of interventions (appropriate indication, including written consent and all potential complications, ruling out anticoagulation, allergies, and local or systemic infection, IV access, full monitoring, trained assistant, and resuscitation equipment)
Position supine on tipping trolley with head ring
Preferably no sedation
Patient should breathe through their mouth and not talk, to prevent swallowing

Technique

Fluoroscopy-guided (anterior approach)

Target is between the vertebral body and the TP (opaque triangle) of C6
Angle the image intensi er slightly caudally to visualize C6 junction
Oblique view to visualize the foramen—needle position away from the vertebral artery and nerve root
Strict tunnel vision for precise needle placement
Contrast is mandatory (live screening)
A total of 5 mL of 0.25% levobupivacaine, preferably with adrenaline, is injected slowly after a 0.5 mL test dose
Sit up the patient to encourage caudal spread
Check successful block—ipsilateral temperature rise of at least 2°C
Horner's syndrome (miosis, ptosis, enophthalmos, conjunctival injection, anhydrosis)
Monitor the patient for at least 30 minutes
Identify if motor or sensory block is present versus selective sympathetic block
Document changes in post-procedure pain score prior to discharge

Ultrasound-guided

Linear, high-frequency US probe
Use of sterile gel, probe cover, and primed needle with injection tubing (Stimuplex®)

Identi cation of the anterior tubercle of C6 (Chassaignac's tubercle)
Ideal placement of the needle tip should be antero-lateral to the longus colli muscle, deep to the prevertebral fascia (to avoid spread along the carotid sheath), but super cial to the fascia investing the longus colli muscle (to avoid injecting into the muscle substance)
More precise injection of a smaller volume of around 4 mL after a 0.5 mL test dose
Assessment of block as under uoroscopy

CT-guided

Not routinely performed

Complications

Arrhythmias (vagal block = bradycardia)
Hypotension
Inadvertent intravascular injection (carotid, vertebral, and inferior thyroid artery), vascular puncture, and haematoma
LA toxicity (seizure)
Hoarseness (recurrent laryngeal nerve—more likely if injected near the carotid sheath)
Horner's syndrome (miosis, ptosis, ipsilateral anhydrosis)
Blocked nose (Guttman's sign)
Motor/sensory de cits (cervical/brachial plexus block)
Phrenic nerve palsy
High spinal (intrathecal injection)
Damage to vagal nerve or parts of the brachial plexus
Pneumothorax
Oesophageal puncture and mediastinitis
Infection—abscesses, meningitis, osteitis
Reaction to drugs or skin prep
Thoracic duct injury

Additional information

The vertebral artery at C7 is unprotected; however, in up to 10% of cases, it may enter the foramen of the transverse process at C5 or higher
Prevent intra-arterial injection with oblique views, gentle aspiration, and contrast media (continuous imaging during injection)—as little as 0.25 mL of LA in the vertebral artery may cause seizure
Stellate ganglion block may not reliably block all sympathetic bres to the hands due to varying contributions of T2 and T3 (Kuntz bres)

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19.3 Splanchnic and coeliac plexus block and neurolysis

Anatomy

Coeliac plexus

The coeliac plexus is one of the three major divisions of the abdominal prevertebral plexus. It is a network of nerves situated retroperitoneally in the upper abdomen anterior to T12–L1 vertebrae

The coeliac plexus lies anterior to the crura of the diaphragm and antero-laterally to the abdominal aorta

The coeliac plexus is composed of a network of nerve bres, from both the sympathetic and parasympathetic systems, including the vagal nerve and contributions from the phrenic nerve and the upper two lumbar sympathetic nerves

Post-ganglionic bres arise from the coeliac plexus and supply the distal oesophagus, stomach, duodenum, small intestine, ascending and proximal transverse colon, adrenal glands, pancreas, spleen, liver, and biliary system

Splanchnic plexus

The sympathetic preganglionic bres from T5 to T12 arise from the infero-medio-lateral grey column of the spinal cord

They travel via the greater (T5–9 spinal roots), lesser (T10, T11), and least (T11, T12) splanchnic nerves, passing over the antero-lateral aspect of the lower thoracic vertebrae (T10–12), to synapse with their post-ganglionic bres in the coeliac plexus

The three splanchnic nerves pass over the lateral border of T11 and T12 vertebrae and carry the majority of nociceptive stimuli from the upper abdominal viscera

They are contained in a narrow compartment de ned by:

- Vertebral bodies—medial
- Pleura—lateral
- Posterior mediastinum—ventral
- Pleura attachment to the vertebra—dorsal
- Crura of the diaphragm—caudal

Indications

To treat visceral pain from the upper part of the abdomen either due to cancer or non-cancer causes

Diagnostic block with LA is used to determine whether the pain is arising from the organs supplied by the coeliac plexus. If adequate relief is obtained after a diagnostic block, neuroablation is then done to provide longer-lasting pain relief

Conditions for these blocks:

- Malignancies of the upper abdomen, e.g. pancreatic carcinoma (most common indication)
- Chronic pancreatitis
- Abdominal angina due to arterial insu ciency
- Pain due to arterial embolization of the liver for cancer therapy
- Acute pancreatitis (LA block only)

A splanchnic nerve block can be tried for non-cancer procedures and when coeliac plexus block (CPB) has failed to provide pain relief

Contraindications

Similar to other interventions

Respiratory insu ciency or pleural adhesions (due to risk of pneumothorax)

Abdominal or thoracic aneurysm

Technique

CPB has been traditionally performed using uoroscopy; however, CT- and US-guided approaches are now being used successfully

Here the transcrural uoroscopic approach for CPB is described

Patient preparation and positioning

The patient is positioned prone, with a pillow under the abdomen

Transcrural approach for CPB

The C-arm is aligned to obtain an AP view of the thoracolumbar region. It is then rotated obliquely to the left, until the tip of the TP of L1 overlies the antero-lateral margin of the L1 vertebral body.

LA is in ltrated into the skin corresponding to the superolateral margin of the L1 vertebra

A 22G, 15 cm needle is inserted at the left superolateral margin of the L1 vertebra

It is advanced under uoroscopic guidance, 0.5 cm at a time, towards the antero-lateral and superior margin of the L1 vertebra, aiming for bone contact

Once bone contact has been established, a lateral view is taken to con rm the position of the needle. The needle is advanced a further 2–3 cm anterior to the L1 vertebra

There is a risk of puncture of the aorta at this stage, in which case the needle is either withdrawn and redirected to lie slightly more laterally or continued through the anterior wall of the aorta (**trans-aortic approach**)

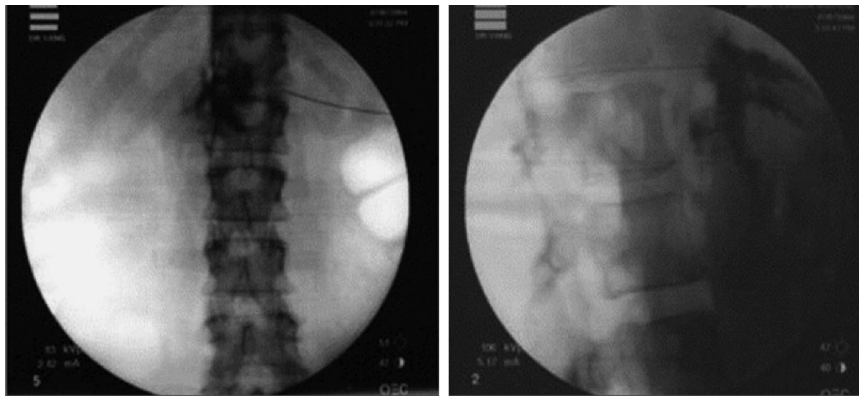
In the AP view, the needle should lie medial to the lateral border of the L1 vertebra. The position is con rmed with 1–2 mL of radio-opaque contrast, which should spread towards the midline, and not beyond the lateral margin of the vertebra in the AP view (see Fig. 19.3.1)

In the lateral view, the contrast should lie anterior to the aorta and must not spread posteriorly towards the nerve roots (see Fig. 19.3.1)

The same procedure is followed on the right side

Amount of drug injected:

- Diagnostic block—10–12 mL of levo-bupivacaine per side
- Neurolytic block—10–12 mL of phenol or alcohol per side



Coeliac plexus block. Left: in the anteroposterior view, the contrast medium extends across the midline. The right needle is inserted superior to the transverse process of L1 towards the T12/L1 interspace. Right: in the lateral view, contrast is owing along the anterolateral border of the aorta and silhouetting the coeliac trunk run-o

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Retrocrural technique for splanchnic nerve block

The T11 or T12 vertebra is identi ed and the endplates are squared in the AP view

The uoroscope is turned oblique about 15° to the side to be blocked

A 22G, 15 cm needle is inserted a little below the rib at the costovertebral junction and advanced to reach the junction of the anterior and middle third of the vertebral body, con rmed in the lateral view

The nal position of the needle is on the antero-lateral margin of the T11 or T12 vertebra, just medial to its lateral border

Radio-opaque contrast is injected to con rm correct needle placement. Spread should be towards the midline, and not beyond the lateral margin of the body of the vertebrae in the AP view (see Fig. 19.3.2)

The same technique is repeated on the opposite side

Amount of drug injected:

- Diagnostic block—5–8 mL of levo-bupivacaine per side
- Neurolytic block—5–8 mL of phenol or alcohol per side

Radiofrequency denervation of the splanchnic nerves

The technique of needle placement for RF denervation is similar to the techniques described above

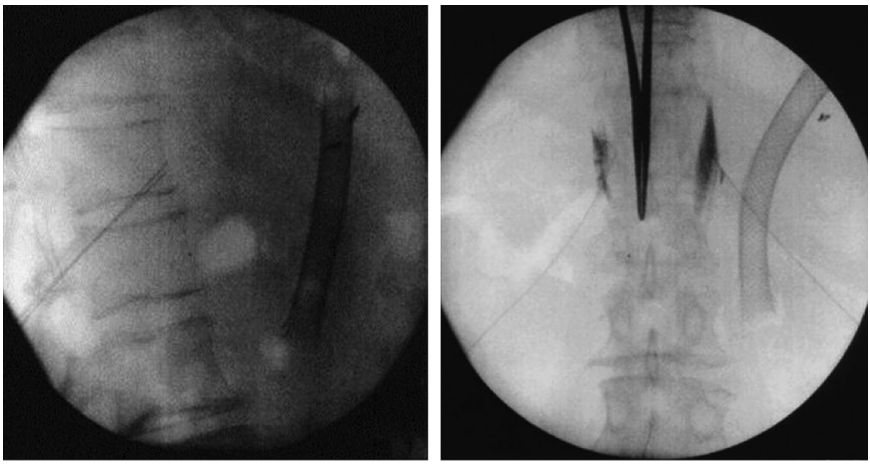
15 cm RF needles with a 10 mm active tip are used

Sensory stimulation should elicit pain and discomfort in the epigastric region of the abdomen

No contractions should be seen on motor stimulation up to 2 V (RF needle at a safe distance from the intercostal nerve)

If the patient reports a band-like stimulation pattern, the intercostal nerve has been stimulated and the needle should be advanced slightly

Neuroablative lesion procedure is similar for all RFs



Splanchnic nerve block. Classic two-needle technique in the lateral view (left) showing the nal needle tip position. Note the spread of contrast is limited to the lateral portion of T12 on the right image

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Complications

Orthostatic hypotension (50% with splanchnic nerve block; 10% with transcrural approach). This is due to blockade of sympathetic innervation

Transient diarrhoea (65% with transcrural approach; 5% with splanchnic nerve block), also due to sympathetic blockade

Pneumothorax is rare, but more likely with splanchnic nerve block than with CPB

Paraplegia, bowel and bladder dysfunction (1 in 700 after neurolytic block). These complications are due to alcohol or phenol causing spasm or necrosis of spinal segmental arteries that supply the spinal cord such as the artery of Adamkiewicz

Intravascular injection. Alcohol injected intravascularly will lead to alcohol levels above the legal limits; however, at the dose it is normally given, it is below severe alcohol toxicity. Intravascular phenol causes features similar to LA toxicity

Backache due to needle trauma, retroperitoneal haematoma. Haematocrit should be measured at serial intervals, and imaging performed if there is a drop in haematocrit

Abdominal aortic dissection, as a result of trauma from the needle

Injury to abdominal organs, gastric perforation, haematuria from kidney injury

Epidural, subarachnoid injection and injury to the nerve roots

Additional information

Radiographic guidance in the form of uoroscopy, CT, or US is of paramount importance, given the nature of risks associated with this block

Needles should always be directed medially towards the antero-lateral margin of the vertebrae. Lateral placement of the needle could cause complications such as organ damage and pneumothorax

Splanchnic nerve block has a higher incidence of pneumothorax, compared to CPB. The risk of pneumothorax can be minimized by keeping the needles close to the vertebral body at all times

A positive diagnostic block is a poor predictor for a negative response to a neurolytic block. The practice of performing a diagnostic block before neurolysis is questionable in patients with terminal malignancy

A review of three RCTs suggested that CPB provides the best results in pancreatic carcinoma without evidence of disease outside the viscera, rather than in advanced pancreatic carcinoma

An RCT revealed that splanchnic nerve RF ablation led to signi cantly better pain relief, QoL, and analgesic consumption, compared to CPB, and may be more suitable for patients with upper abdominal pain from non-malignant causes such as chronic pancreatitis. This is because of the predictable anatomy of the splanchnic nerves, allowing accurate placement of the RF needles

Evidence

CPB for pain secondary to pancreatic cancer—1A

CPB for pain secondary to chronic pancreatitis—2C

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19.4 Lumbar sympathetic block and sympathectomy

Anatomy of the lumbar sympathetic ganglia

The target is L1–5 paravertebral sympathetic ganglia

The L1 and L2 sympathetic ganglia are often fused; hence, there is often only four paired lumbar sympathetic ganglia

Anterior to the medial origin of the psoas muscle

Lie on a craniocaudal line connecting the antero-lateral border of the vertebral body

The relationship of the ganglion is most consistent at the middle to upper third of the L3 vertebral body in the lateral view

At L2 level, the ganglion is often at the lower third of the vertebral body in the lateral view

At L4 and L5 levels, this relationship is more variable

The vena cava lies anterior to the chain on the right side, and the aorta is antero-medial on the left side

Indications

Phantom limb pain, neuropathic pain, CRPS, and pain from severe cold exposure in the lower limbs

Vascular abnormalities such as Raynaud's disease, Berger's disease, and arteriosclerotic peripheral vascular disease

Miscellaneous: hyperhidrosis, erythromelalgia

Contraindications

Lack of informed consent, patient refusal

Infection

Coagulopathy

Anatomical anomaly of the lumbar spine

Patient preparation and positioning

The patient is positioned prone on an X-ray table, with a pillow under the abdomen to neutralize the lumbar lordosis

Technique—general principles

Lumbar sympathetic ganglion interventions are usually done in two stages

Initially a diagnostic block is performed

If e ective in symptom management and improving QoL, the following can be considered:

- The procedure can be repeated
- RF ablation can be considered
- Neurolytic injection (alcohol/phenol) in cancer pain or palliative conditions

The procedure is best done at L3 level

Technique of procedure

AP view of lumbar vertebrae

Count up from L5 and identify L2, L3, and L4 vertebrae

The vertebra in focus is squared by either a caudal or sometimes a cranial tilt of the uoroscopy tube to eliminate the double edge of the inferior border of the vertebral body, which should be visualized as a largely single line

An oblique ipsilateral tilt of the uoroscopy tube to the side of the block is then done. Su cient tilting to obscure the TP projection within the vertebral body will help achieve an extraforaminal needle path, avoiding nerve root injury and genitofemoral neuralgia during RF ablation

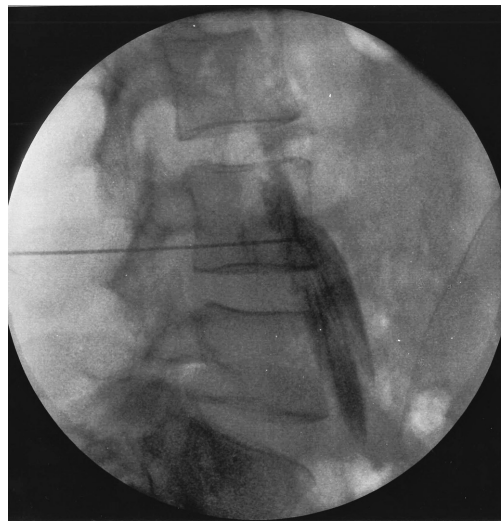
The nal target is the antero-lateral margin in the transverse plane of the lower quarter of the L2 vertebral body, the upper quarter of the L3 vertebral body, or the middle of the L4 vertebral body in the lateral view of uoroscopy

The needle entry point is at the lateral border of the vertebral body projection in the oblique view and at the appropriate level of the vertebral body according to the preceding point

The needle is inserted along the X-ray beam (gun barrel approach)

The position of the needle should be adjusted to achieve this in the super cial planes

After insertion of the needle to a few centimetres deep, a lateral view is used to con rm the distance from the foramen (a craniocaudal tilt is best left undisturbed in the lateral view)



Final needle position in the lateral view, but contrast delineates the striated myogram of the psoas muscle. The needle is advanced antero-medially

Once the needle approaches the posterior edge of the foraminal projection, the needle should be advanced carefully, looking for paraesthesiae due to contact with the nerve root. If this is encountered, then the needle should be angled superiorly or inferiorly to pass the nerve root safely

The needle is then advanced in the lateral view to the anterior edge of the vertebral body

In the AP view, the needle should be medial to the lateral projection of the vertebral body on the side of the block

Switching again to the lateral view, a small amount of contrast is injected. This should spread anterior to the vertebral body in the retroperitoneal space and has a typical vacuolated appearance

If there is posterior spread with a typical striated appearance of muscle, this implies that the needle is within the psoas muscle. The needle should be carefully advanced by a few millimetres to lie anterior to the muscle, to avoid a lumbar plexus block or thermal/chemical injury to the plexus (see Figs. 19.4.1 and 19.4.2)

Diagnostic block

A total of 10–15 mL of LA (levo bupivacaine or ropivacaine) at L3 level, aiming for LA spread to cover L2–4 levels

May need multiple-level injections for adequate LA spread

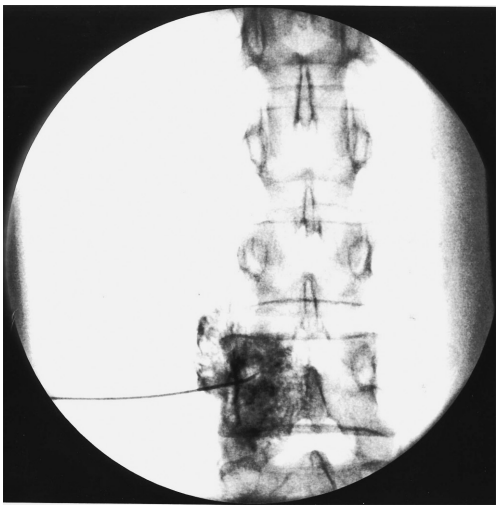
Chemical neurolysis

6–10% phenol or alcohol 50–100% with contrast can be used for chemical neurolysis

It is best done with small volumes at multiple levels

Radiofrequency thermal neurolysis

A 20G curved, blunt needle with a 5 mm active tip is preferred to minimize vascular puncture and nerve root injury



Final needle position in the AP view. Contrast delineates the correct vacuolated appearance of retroperitoneal tissue

After needle positioning, as discussed, sensory stimulation at 50 Hz would elicit a deep ache in the abdomen and no paraesthesiae in the lumbar plexus distribution

Motor stimulation at 2 Hz should not elicit muscle contractions in the lower limb (femoral and obturator nerve supply)

A total of 5 mL of 0.25% levo-bupivacaine or 0.2% ropivacaine with dexamethasone is injected prior to the lesions

Lesions at 80°C for 60–90 seconds at L2, L3, and L4 levels

Complications

Quoted risk of 4–15% of genitofemoral neuralgia after therapeutic chemical or RF sympathectomy (highest risk if procedure performed at L4)

Disc puncture and discitis

Radicular artery injury and paraplegia

Ureteric injury

Impotence

Retroperitoneal haematoma

Hypotension and diarrhoea

Infection and LA toxicity

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19.5 Hypogastric plexus block

Anatomy

The hypogastric plexus is an extension of the sympathetic (superior hypogastric plexus) and parasympathetic ANS (inferior hypogastric plexus) (see Fig. 19.5.1)

The superior hypogastric plexus lies anterior to the lower third of the L5 vertebral body and the upper third of S1. It mediates most nociceptive visceral stimuli from the pelvic organs

The inferior hypogastric plexus lies at S2–4, surrounding the rectum

Indications

Non-gynaecological pain: PHN (sacral region)

Gynaecological pain: endometriosis, vulvodynia, pelvic tumour

Pain involving the bladder, penis, vagina, rectum, anus, and pelvis

Patient positioning

Prone position, pillows under the hips and ankles

Technique—superior hypogastric posterior approach

Determine the L5/S1 interspace using uoroscopy guidance in the AP view

Rotate the C-arm in a cephalad/caudad direction to ensure the vertebral endplates are aligned

Rotate the C-arm ipsilaterally in the oblique plane to visualize the lateral vertebral body, ensuring the end of the TP is on the anterior aspect of the vertebral body

Position to aim for: mid/anterior aspect of the lower third of the L5 vertebral body

LA to skin entry point using a 23G, then 21G needle

A 20G, 15 cm curved tip to be inserted using the perpendicular needle trajectory technique to the C-arm

When the vertebral body is struck, visualize in the AP view to con rm needle position

Rotate the C-arm to the lateral position and rotate the needle, advancing gently

A 'give' should determine the needle position anterior to the vertebral body

Con rm the needle position in the lateral and AP views

Aspirate to ensure no vascular injection; contrast injection should demonstrate spread inferiorly and superiorly to the anterior of the vertebra

Inject LA/steroids once you have achieved con rmation of spread

Repeat for the contralateral side

Complications

Common: sympathetic nerve block causing diarrhoea, hypotension

Rare: infection, bleeding (aortic/vena cava puncture), nerve injury, LA toxicity, visceral organ injury

Special points

The procedure can also be performed with:

- Superior hypogastric plexus block with a postero-medial transdiscal or anterior approach, with the aid of US, uoroscopy, or CT guidance
- Inferior hypogastric plexus block with a coccygeal transverse or trans-sacral approach

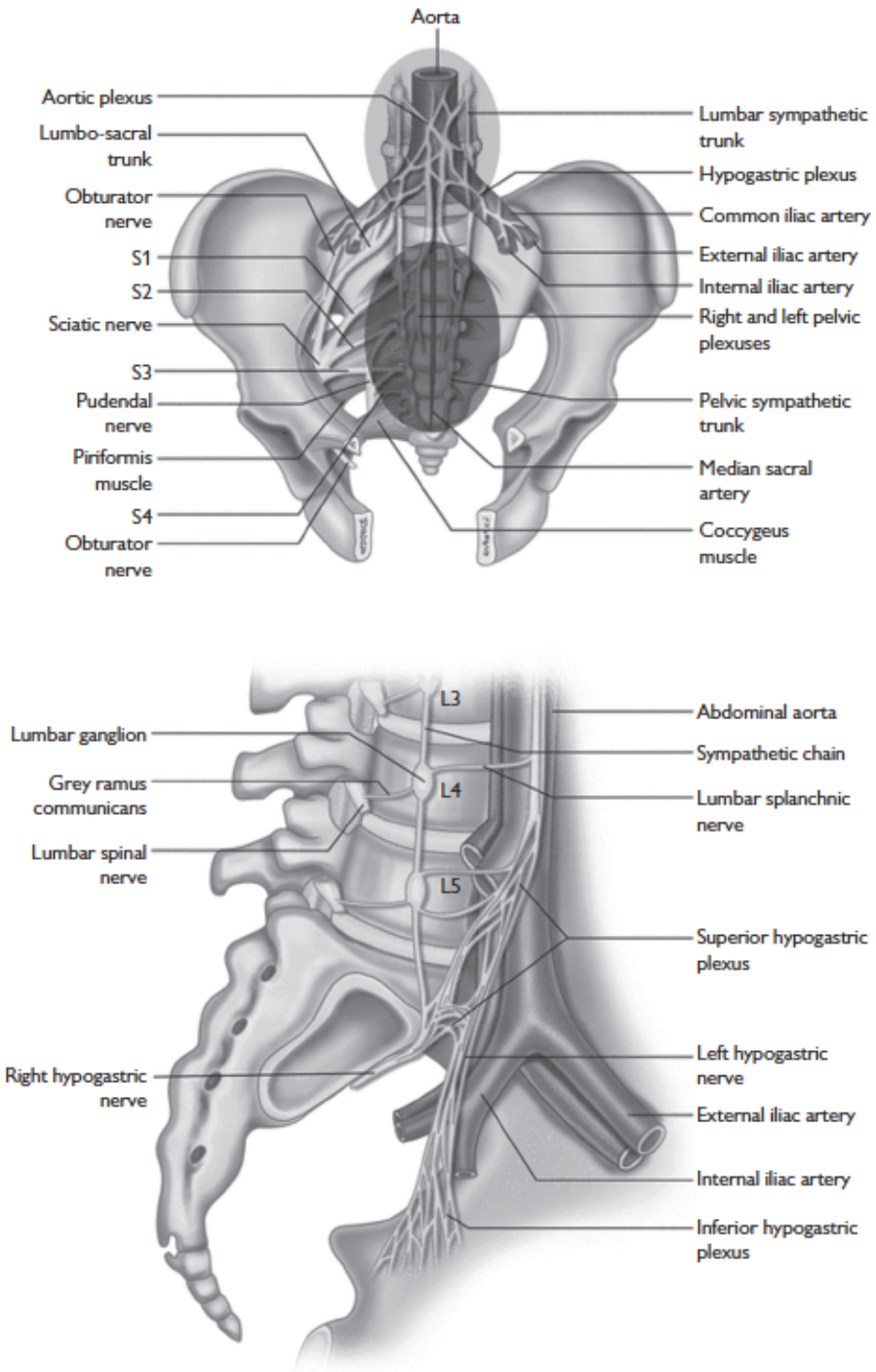


Figure 19.5.1 Hypogastric plexus

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CHAPTER 20

Spinal Cord and Neuromodulation

Sangeeta Das, Gustav Jirikowski, Yehia Kamel, Deepak Malik, Manish Mittal, Yin Yee Ng, Stefano Palmisani, David Pang, Jan Rudiger, and Athmaja Thottungal

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20.1 Anatomy of the spinal cord

De nition

The spinal cord is part of the CNS

Connection between the brain and the peripheral nervous system

32 segments: eight cervical, 12 thoracic, ve lumbar, ve sacral, two coccygeal

Grey matter

(See Figs. 20.1.1 and 20.1.2.)

Numerous nerve cells and their connections form the core, which shows bilateral symmetry

It contains cell bodies of second-order sensory a erents in the dorsal horn (DH), autonomic nerves (intermediate column), and motor e erents in the ventral horn (VH)

Dorsal horns (DHs)

Entry for sensory nerve bres which originate from DRGs.

Important for perception of pain, tactile stimuli, proprioception, etc.

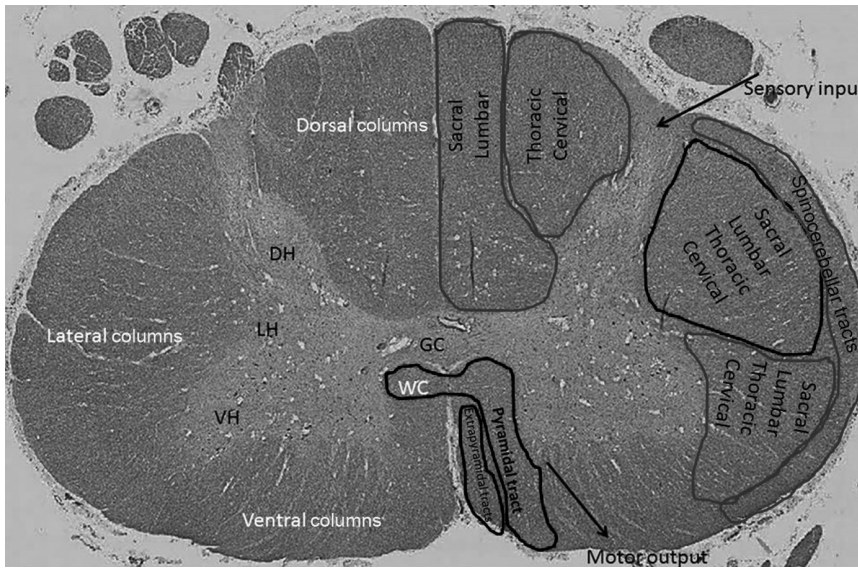
The dorsal horn includes the nucleus dorsalis, nucleus proprius, and stellate ganglion

Lateral horns (LHs)

Part of the sympathetic nervous system. The LH is absent in cervical segments

Dorsal LH has viscero-sensory properties, and ventral LH controls viscero-motor functions

Interneurons control visceral re exes



Histological cross-section of the spinal cord. Grey matter: DH, dorsal horn; GC, grey commissure; LH, lateral horn; VH, ventral horn; WC, white commissure. White matter: ascending tracts in black; descending tracts in grey

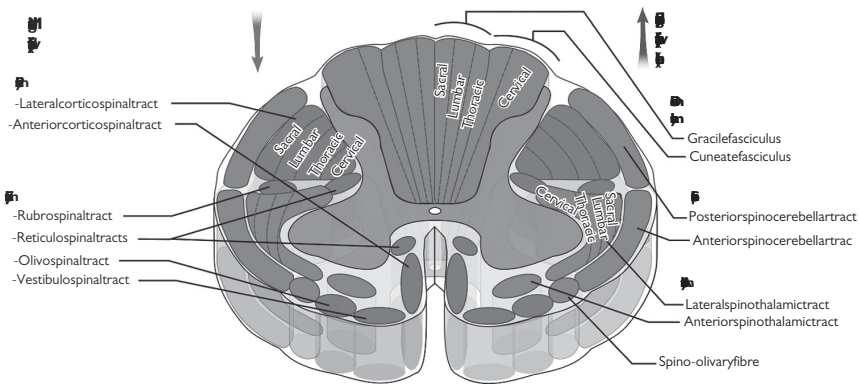
Ventral horns (VHs)

Contain motor nuclei

Alpha motor neurons innervate skeletal muscles, and gamma motor neurons supply muscle spindles. Their axons form the anterior root as part of the spinal nerves

Monosynaptic and polysynaptic re exes

Grey matter neurons are interconnected. Connections between the DH and VH are the basis for **monosynaptic (somato-motor) re exes**



Spinal cord tracts

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Grey matter of both sides of the spinal cord is interconnected by the **grey commissure (GC)**. This is the basis for **polysynaptic re exes**. Involvement of the LH controls **visceral re exes**

Reticular formation

Connection of all portions and all segments of the grey matter; important for all sensory and motor functions. Highly signi cant for perception of pain

The centre of the GC hosts the central canal. Neurons that surround the reticular formation extend processes through the ependyma

White matter

Bundles of myelinated neuronal bres leading to blue: dorsal column, spinocerebellar tracts, anterolateral system and from red: pyramidal and extrapyramidal tracts the brain (see Fig. 20.1.2). They surround the grey matter and show somato-topic organization

Dorsal columns

Contain ascending sensory nerve bres to the medulla oblongata

The fasciculus gracilis hosts a erents from sacral, lumbar, and thoracic segments; the fasciculus cuneatus contains upper thoracic and cervical a erents

Lateral columns

Contain lateral spinocerebellar tracts, and descending corticospinal = pyramidal (red) and ascending spinothalamic tracts (blue)

Ventral columns

Contain descending bres of the extrapyramidal system, including rubrospinal, olivospinal, vestibulospinal, and reticulospinal tracts

White commissure

Only cervical segments have a **white commissure (WC)** which contains bres of the pyramidal tract prior to crossing to the contralateral side

Blood supply

One ventral (two-thirds) and two dorsal arteries (one-third) provide oxygen to the entire spinal cord

The cervical segments are supplied from branches of the vertebral arteries. All other segments are supplied from the aorta via intercostal arteries.

Numerous anastomoses interconnect spinal arteries

Spinal veins drain into venous plexuses along spinal nerves

Clinical signi cance

Destruction of the grey matter results in permanent motor and/or sensory impairment of the respective segment, depending on the extent of the lesion

Destruction of the white matter causes paralysis of all segments caudal to the lesion. Due to increased excitability of motor neurons, such paralysis eventually becomes spastic

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20.2 Anatomy of vertebral bodies

Shape of a typical vertebral body

Cylindrical body
Superior and inferior vertebral endplates
Anterior and posterior longitudinal ligaments
Horizontal view—convex anteriorly, concave posteriorly
Sagittal view—concave anteriorly, at posteriorly

Blood supply

Paired segmental arteries
Posterior venous drainage into internal and external vertebral venous plexus, then into regional segmental veins (vertebral, posterior intercostal, lumbar, sacral), then into the central venous system
Free anastomoses, valveless venous communication to pelvic, renal, and azygos venous systems aid haematogenous disease spread, including infection and malignancy

Innervation

Sinu-vertebral branches
Via endplates; also gives some innervation to intervertebral discs
Interosseous nerves follow the vasculature

Lymphatic drainage

Details unknown
Likely deep lymphatic vessels following arteries

Vertebral endplates

Thin hyaline cartilage layer with supporting cortical bone plate
Supports intervertebral discs
Fracture risk centrally as weak, superior more than inferior

Cervical vertebrae

Seven cervical vertebrae
Vertebral artery traverses via foramen transversarium, except in C7
C1/atlas: ring-shaped, no true body or spine, anterior spinal canal facet for dens articulation
C2/axis: body with dens overlying superiorly, held against C1 'body', allowing rotation of the head
C3–6: small body, wider in the transverse than in the AP plane, at lamina, bi d spinous process
C7/vertebra prominens: more similar to thoracic vertebrae, non-bi d spinous process, foramen transversarium traversed by venous and post-ganglionic sympathetic plexuses

Thoracic vertebrae

Twelve thoracic vertebrae
T1: atypical, more similar to C7, longer upper rib facet joint, smaller lower rib facet joint
T2–T8: heart-shaped body, with small costal demi-facet joint on superolateral border (for rib at same level) and larger costal demi-facet joint infero-laterally (for rib at level below)
T9–12: single superior costal facets

Lumbar vertebrae

Five lumbar vertebrae
Large kidney-shaped body, short pedicles, without foramina transversaria and costal facets
L5 body wedge-shaped for weight loading; higher anteriorly, forming lumbar lordosis

Sacrum

Five vertebral bodies fused to form a large triangular sacrum with a concave ventral surface
Central axis of pelvic girdle between the two iliums, forming the sacroiliac (SI) joints
Sacral promontory articulates with L5 cranially
Inferior oval facet for articulation with coccyx

Coccyx

Small triangular bone/rudimentary tail made of 4–5 fused coccygeal vertebrae
Directed infero-ventrally from sacral apex
Orientation may vary and can be mobile

Pathologies in vertebral bodies

Degenerative, e.g. OA, spondylosis, spondylolisthesis
Trauma/vertebral fracture
Malignancy (primary or secondary)
Infection
In ammatory
Metabolic, including osteoporosis
Vascular malformations

Radiological investigations

X-ray and computed tomography

Used for bony changes, including:
- Misalignment, e.g. scoliosis, antero-/retrolisthesis, pars defect
- Fracture
- Sacralization of L5 vertebra

X-ray less useful as likely normal with high false positive rate; CT useful if MRI contraindicated

Magnetic resonance imaging

Used for soft tissue changes
May demonstrate changes of unknown signi cance, e.g. Schmorl's nodes, Modic changes

Bone scans

Technetium-99 scan: identifies inflammatory processes in bone which can be from pathologies such as cancers (primary or secondary), infections, and fractures

SPECT: localizes lesions which can be malignant (e.g. in facet joints, pedicles, spinous processes, vertebral bodies) or secondary to other inflammatory processes

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20.3 Discography

Introduction

Chronic discogenic back pain has a prevalence of 35–40%

Due to low sensitivity and specificity of clinical diagnosis and the presence of asymptomatic disc changes seen with conventional imaging methods, i.e. MRI, invasive methods such as provocative discography, in combination with post-discography CT, can be used to diagnose discogenic pain

Anatomy

The intervertebral disc has four distinct regions

Nucleus pulposus

It forms the gelatinous core of the disc and contains collagen and elastin fibres embedded in proteoglycan matrix

Main function is to maintain disc hydration

Annulus fibrosus

Thick outer ring of fibrous cartilage made of 15–25 concentric rings or lamellae, with collagen fibres lying parallel to individual lamellae and elastin fibres in between the lamellae (they assist in preserving the disc shape)

Vertebral endplates

Thin layer of hyaline cartilage that articulates between the disc and vertebral body

Nerve supply of intervertebral disc

In a normal disc, only the outer third of the annulus fibrosus and vertebral endplates are innervated, but in discogenic pain, this innervation extends to the inner third and even to the nucleus pulposus via vascular granulation tissue after healing of annular tears

The anterior and lateral annulus fibrosus is supplied by grey rami of the sympathetic trunk, and the posterior is supplied by the recurrent sinu-vertebral nerve, formed by a branch from the ventral ramus and grey rami

Indications

Persistent severe symptoms when other diagnostic tests were inconclusive

Assessment of disc prior to fusion to identify the symptomatic disc and whether the adjacent disc can support the fusion

Evaluation of abnormal disc or recurrent pain from a disc that was previously operated on

Failed back surgery or a di erent source of back pain

Assessment of candidates for minimally invasive surgery, with con rmed disc herniation

Contraindications

As with other interventions

Substantial psychosocial stressors or poorly controlled mood disorders

Solid bone fusion

Severe spinal canal compromise

Patient preparation and positioning

Standard protocol followed

Strict asepsis, under X-ray uoroscopy

The patient is positioned prone, with the C-arm oblique, to align the facet joint in the middle of the uoroscope screen

Technique—lumbar discography

LA in ltration (e.g. lidocaine 1%) for skin in ltration; avoid excessive use to prevent anaesthetizing the sinu-vertebral nerve and ramus communicans

Introduce the needle just above the lateral margin of the superior articular process

The introducer needle is then advanced just over the lateral edge of the superior articular process or to the margin of the disc

After con rming the introducer needle position on the lateral view, a 25G, 15cm discogram needle is slowly advanced into the centre of the disc through the introducer needle, while monitoring the lateral view

The disc is slowly pressurized by injecting 0.5 mL increments of contrast through a syringe attached to a pressure-measuring device, while recording the opening pressure, injection pressure, location of the contrast medium, and evoked pain response

End points

Intradiscal pressure of 80–100 psi above the opening pressure with a normal-appearing nucleogram

3.5 mL of contrast has been injected

Diagnostic criteria (Spine Intervention Society)

Provocation of the suspect disc induces concordant pain

The pain is at least 7/10 on NRS

The pain is provoked by <50 psi above the opening pressure in a disc with a grade 3 annular tear

Provocation of at least one adjacent disc does not induce concordant pain

Four-type classi cation by Derby et al. in respect to annular sensitivity

Discs which are painful at pressures <15 psi above the opening pressure are termed low-pressure positive or 'chemically sensitive' discs

Discs which are painful at pressures between 15 and 50 psi are termed 'mechanically sensitive' discs

Indeterminate discs are painful at pressures between 51 and 90 psi

Normal discs are not painful on provocation

Interpretation of post-discography CT

Depicts vertebral disc architecture

Modi ed Dallas discogram scale to classify post-CT ndings

Grade 0 describes contrast contained within the nucleus

Grades 1–3 describe the degree of ssuring extending to the inner, middle, and outer annulus, respectively

Grade 4 describes a grade 3 annular ssure with >30° circumferential arc of contrast.

Grade 5 annular tear indicates rupture or spread of contrast beyond the outer annulus

Complications

Bacterial discitis (0.25% per patient and <0.14% per disc)

Meningitis, arachnoiditis, epidural abscess

Acute disc herniation, spinal headache/CSF leakage, intrathecal (IT) haemorrhage

Retroperitoneal bleeding, pulmonary embolism from nucleus pulposus material

Allergic reaction

Seizure

Special points

Discography performed in accordance with current standards in appropriately selected patients is a safe and useful diagnostic tool to inform treatment decisions

Lumbar discography can be a useful tool in assessing chronic back pain

Weak evidence for cervical, and no evidence for thoracic back pain

Further reading

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20.4 Dorsal root ganglion

De nition

Cluster of nerve cells

Interface between the peripheral and central nervous system

Port of entry of peripheral inputs (somato-sensory, proprioceptive, viscero-sensory, nociceptive)

Contains the cell bodies of the rst-order sensory neurons (pseudo-unipolar ganglion cells) which are engulfed by satellite cells

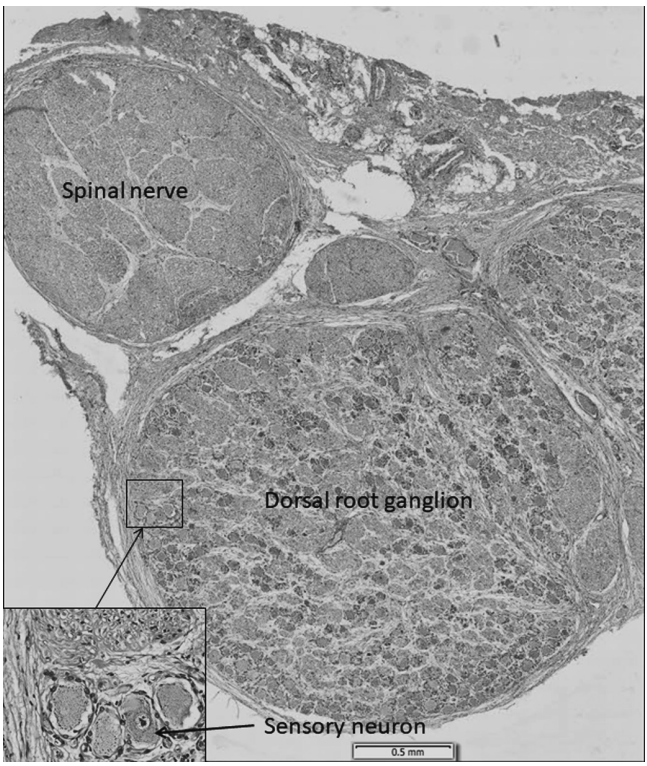
DRGs are encapsulated by a layer of dense connective tissue that connects with the dura mater of the spinal cord

Localization

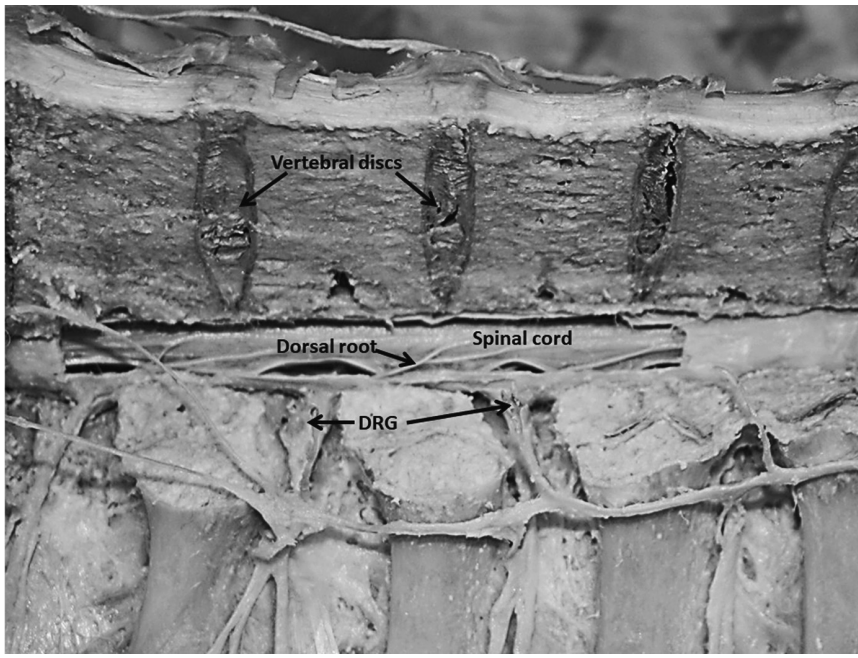
(See Figs. 20.4.1 and 20.4.2.)

DRGs are associated with spinal nerves

DRGs are part of the peripheral nervous system, derived from the neural crest



Histological image of the dorsal root ganglion and spinal nerve root, with subsection demonstrating the sensory input



Macroscopic image of the dorsal root ganglion (DRG) in relation to surrounding structures

They are located in the intervertebral foramina

DRG neurons project to 2nd ONs in the DH of the spinal cord

A erents connect DRG neurons via myelinated dendrites with either dermatomes or myotomes, or with visceral organs

Function

Somato-sensory perception

Speci c innervation of receptors within dermatomes (Merkel bodies, Vater–Paccini bodies, Ru ni bodies, free nerve endings). Important for perception of pain, heat, cold, pressure, movement, and tactile stimuli

Viscero-sensory perception

Free nerve endings in visceral organs are sensory dendrites of DRG neurons (intestinal pain, cardiac pain, fullness of urinary bladder or rectum)

Motor control

DRG neurons innervate proprioceptors (muscle spindles, Golgi tendon organs, kinaesthetic joint receptors)—important for re exes

Drainage of cerebrospinal uid

Peri-ganglionic venous plexuses are important for CSF resorption and CSF current

Functional impact—pathophysiology

Loss of somatic re exes: indicative of interrupted neuronal circuits of either peripheral nerves, DRGs, or the spinal cord

Loss of sensation of speci c dermatomes, e.g. as a consequence of a ruptured vertebral disc

Head zones: somato-sensory and viscero-sensory neurons represent distinct groups of cells within the DRG. Their axons terminate on identical neurons in DH nuclei. Brain circuits can recognize visceral pain as somato-sensory pain. Therefore, visceral pain can be experienced as somatic pain in certain dermatomes (see 26.1. Overview of visceral pain, p. 527)

Viral infections can speci cally a ect sensory spinal nerves and DRGs (e.g. herpes zoster)

Diagnostic tests

Sensory tests of dermatomes

Help to determine the extent of damage to a peripheral nerve

Re ex tests

Stimulation of proprioceptors

Axons of DRG neurons terminate on interneurons in the spinal cord which innervate motor neurons to trigger re exes

Sensory neurography

Measurement of sensory nerve action potentials (SNAPs)

Histamine test

Failure to develop redness of skin at the injection site indicates dea erentation

Clinical relevance

DRG injections block sensory supply of a speci c spinal nerve without motor impairment

Neurostimulation of DRG neurons can be useful in chronic neuropathic pain

Chronic pain: injuries can cause maladaptive molecular changes in DRG neurons, resulting in hypersensitivity and hyperexcitability

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20.5 Epidural injections

Introduction

Epidural injections are used in chronic spinal pain and can be a useful part of multidisciplinary care

Careful patient selection, and it is important that it is o ered as part of a package of care, and not as a stand-alone treatment

Epidurals do not cure the underlying pathology but are a useful temporary analgesic modality to allow for natural resolution or to facilitate other pain management strategies (e.g. physiotherapy)

Di erent approaches are available—the aim is to deposit LA and steroid to the DRG or the nerve root that is a ected by spinal pathology (e.g. prolapsed intervertebral disc or foraminal stenosis)

Indications

Nerve root in ammation or compression with spinal radicular pain that has not responded to conservative management

Nerve root compression on imaging is common, but there must be a clear clinical correlation with symptoms and signs of nerve root irritation

A large network meta-analysis did show that ESI was e ective in lumbar radicular pain

However, it is not indicated in axial low back pain without radicular features

Contraindications

Patient refusal

Local infection and coagulopathy

Severe central spinal stenosis

Adverse reaction to LA or steroids

Applied anatomy

As the nerve roots and DRG exit the spinal cord, they are initially located in the epidural space

Therefore, nerve irritation caused by a prolapsed intervertebral disc or spinal OA and degenerative changes can be treated with an injection into the epidural space

Many trials of ESIs are awed by poor methodology and by poor reporting on whether the medication was injected in the correct place

LA and steroids can exert both an analgesic and an anti-in ammatory e ect

Technique

Strict aseptic technique and image guidance with radiographic contrast are mandatory

The approaches to the epidural space are:

- Interlaminar
- Transforaminal
- Sacral hiatus/caudal
- Catheter techniques and epidurolysis

The transforaminal approach has the advantage of depositing LA and steroid in the anterior epidural space, which is closer to the source of pathology

However, the transforaminal approach is technically more di cult, and there is a risk of nerve injury by direct needle trauma or vascular injury

If steroids are used, they must be non-particulate since injection in nutrient arteries has been associated with spinal cord infarction

IV access is secured prior to the procedure, and the skin is disinfected

Patients are usually positioned prone to allow optimal uoroscopic imaging

A lateral approach is sometimes used for lumbar and caudal epidurals

Full aseptic technique must be used at all times (including sterile gloves and gown, hat, and mask)

Interlaminar

Loss of resistance technique with Tuohy needle and saline (or air)

Needle placement is in the space between the vertebral bodies/laminae

A paramedian approach is preferred to improve steroid deposition in the antero-lateral epidural space

For the cervical approach, a contralateral oblique approach can be useful

Transforaminal

Under uoroscopic imaging, the needle is directed to the intervertebral foramen

Care must be taken to avoid nerve injury as the needle is placed very close to the nerve root

Minimal or no sedation is recommended, and a blunt (non-curved) needle is recommended if available

This approach is recommended for lumbar epidurals

A transforaminal approach for the cervical area risks nerve and vascular injury and should be performed by experienced operators only

Sacral hiatus/caudal approach

The lumbar epidural space can be accessed via injection at the sacral hiatus which is where the epidural space terminates inferiorly

Using a large volume, it is possible to deliver injectate to the lumbar nerve roots

Usually technically simple, with a low risk of dural puncture

Catheter techniques/epidurolysis

One of the challenges is to ensure delivery of steroid precisely to the pathological area

Using a blunt steerable catheter in the epidural space can allow precise targeting of nerve roots (see 20.6 Lumbar epidural adhesiolysis, p. 380)

In addition, if there is epidural brosis or lling defects that may represent obstruction, the injectate may not reach the desired target

Entry into the epidural space with an introducer needle with a circular cross-section and the catheter placed through with a needle-through-needle technique

For the lumbar area, the sacral hiatus is used, but for thoracic and cervical areas, the introducer is placed using an interlaminar approach

The catheter is steered under uoroscopy to the antero-lateral epidural space at the site of pathology

It is important not to force the catheter through any obstruction, but to use hydro-dissection if there are any lling defects

Complications

Dural puncture (approximately 0.5–1%) that may cause post-dural puncture headache

Nerve injury (make sure that there is contrast run-o outside the spine, so that the injected volume does not compress the spinal cord)

Epidural haematoma

Infection and epidural abscess

Vascular injection (avoid particulate steroids using a translaminar approach—the particulate component causes embolic infarcts into the spinal arteries; that risk is minimized with the use of non-particulate steroid and blunt needles)

Further reading

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20.6 Lumbar epidural adhesiolysis

Anatomy

Both techniques (percutaneous and endoscopic technique) target the lumbar epidural space

Basic knowledge of lumbar spine anatomy and its visualization under uoroscopy is required

Indications

Chronic lower back pain with or without radiculopathy

Especially in the context of previous spine surgery, spinal stenosis, and epidural scar tissue (demonstrated with either contrast-enhanced MRI or epidurogram under live uoroscopy)

Contraindications

Bleeding disorders

Antiplatelet/anticoagulation therapy

Headache disorders not appropriately investigated (*endoscopic adhesiolysis only*)

Vision disorders (*endoscopic adhesiolysis only*)

Patient preparation and positioning

Prone position (support in the abdominal area to straighten the lumbar lordosis)

Full sterile preparation for both the patient and the operator

Antibiotics are not required

IV access is mandatory (for safety reasons), even if sedation is not administered

Technique

Both techniques require cannulation of the sacral hiatus under uoroscopy (lateral and AP view) to access the posterior epidural space

Percutaneous adhesiolysis

The original technique involves the identi cation of epidural lling defects (epidurogram)

Placement of a spring-tip radio-opaque catheter in the area of the defect and multiple injections of a mixture of drugs to facilitate adhesiolysis:

Day 1 (hyaluronidase, bupivacaine, triamcinolone, 10% sodium chloride)

Days 2 and 3 (bupivacaine and 10% sodium chloride)

A modi ed technique seems to be equally e ective despite being a single-day procedure, the use of short-acting LA and non-particulate steroids, and the overall reduction in volume of the injectate

No strong evidence showing substantial bene ts of 10% saline versus 5% or 0.9%

Bene ts of the procedures are believed to be secondary to dissolution of adhesions (uncon rmed), prevention of recurrence through inhibition of broblasts, and greater access for analgesic substances in the perineural spaces

Endoscopic adhesiolysis

The endoscopic technique requires a exible steerable endoscope to explore the postero-lateral epidural space around the dura, and to visually identify pathological scar tissue and remove it using mechanical (Fogarty-like balloon) or thermal (RF probe) tools that are inserted through one of the working channels of the endoscope

Most practitioners do not inject drugs at the end of the procedure

Bene ts of the procedures are believed to be secondary to mechanical and/or thermal lysis of adhesions (con rmed under direct vision)

Complications

Epidural bleeding—very rare

Dural tear—4% (*percutaneous)* to 8–10% (*endoscopic)*

Post-procedural headache

Potential for trauma to the nerve roots, mass e ect of the high volume of injectate causing transient or permanent neurological de cits

Temporary or permanent visual disturbances (*endoscopic adhesiolysis only*)—very rare

Allergic reaction to any of the drugs used (*percutaneous adhesiolysis only*)—very rare

Shearing of the catheter (*percutaneous adhesiolysis only*)

Additional information

Percutaneous adhesiolysis

Use of epidurogram to guide treatment

Try to inject part of the drug mixture in the lateral epidural space to ensure adequate spread towards the anterior epidural compartment

Use contrast dye injection under live uoroscopy prior to injection of any drug, to detect intravascular or subarachnoid spread

If using hypertonic saline, rst inject an LA test dose and assess neurology at 15 and 30 minutes to detect subdural/IT catheter tip positioning

Endoscopic adhesiolysis

To avoid the risks related to saline over-infusion, monitor carefully the volume injected (usual range 80–300 mL); volumes above 100–150 mL require an awake patient to monitor the onset of neck discomfort, the rst sign of over-infusion

To distinguish between pathological and non-pathological brous tissue, it is useful to 'probe' the tissue either with the tip of the scope or with one of the surgical tools available to elicit pain which is concordant with the subject's usual pain

Further reading

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20.7 Percutaneous cordotomy

Introduction

This involves the use of RF to ablate the sensory bres of the lateral spinothalamic tract

It is used in refractory cancer pain that is unilateral and below the fourth cervical dermatomal level

Although bilateral cordotomy can be performed for bilateral pain, it is associated with a greater risk of complications and is less commonly done

Recommended if life expectancy is less than 12 months

Refractory incident and neuropathic pain are good indications, but dea erentation pain responds poorly

There are no RCTs evaluating its use and evidence is based on case series

A small proportion of patients with cancer-related pain do not get satisfactory analgesia with systemic medication and cordotomy can provide a useful means of achieving analgesia

Indications

Chest wall pain from malignant mesothelioma

Unilateral limb pain

Other unilateral chest wall pain

Pain from brachial plexus lesions

Contraindications

One of the di culties is that patients are referred late for a cordotomy and the disease may be too advanced

The patient must be able to lie supine for about 60–90 minutes

Coagulopathy

Respiratory distress

Localized infection

Applied anatomy

Cordotomy involves an RF lesion in the lateral spinothalamic tracts that correspond to the painful area

The lateral spinothalamic tracts lie in the antero-lateral quadrant of the spinal cord (they carry contralateral pain and temperature sensation) (See 20.1 Anatomy of the spinal cord, p. 367)

An important anatomical structure is the dentate ligament that is used to identify the midline of the spinal cord

Lesions must be placed anterior to this structure as the spinothalamic tract lies just anterior to it

The lesion is done at C1/2 as it allows needle placement to lesion the lateral spinothalamic tract high enough to result in analgesia from the level of C4 downwards

Lesioning at the lateral spinothalamic tract reduces pain and temperature sensation, with preservation of motor function, touch, and proprioception

Technique

The most common approach is the percutaneous approach using LA or conscious sedation

An open surgical approach is an alternative but requires a laminectomy and is more invasive with the requirement of intraoperative wake-up testing

CT guidance is another alternative with the advantage of easier needle placement at the expense of a longer procedure duration

Patient positioning is supine and due to crossover of the sensory pathways, the lesion must be done in the spinothalamic tract contralateral to the painful area

IV access is mandatory and the head is restrained using either a Pounder or Rosomo headrest

An RF needle with a 2 mm tip is placed under uoroscopic guidance at C1/2 in the lateral view until CSF is encountered

Radiographic contrast is injected to con rm needle placement anterior to the dentate ligament to ensure correct direction of the needle; then the electrode is inserted through this needle

Once the electrode is inserted, the RF machine will show a low impedance as the tip is still in the CSF

Advancing the needle into the spinal cord will result in an increase in impedance, and once in the spinal cord, both motor and sensory testing are performed to check that the electrode is in the correct position to create a lesion in the spinothalamic tract

Motor stimulation at 2 Hz will elicit local ipsilateral neck muscle twitching, but any contralateral limb movement suggests that the tip is at the corticospinal tract and the needle must be repositioned to avoid damage to the motor bres (2 Hz stimulation is to con rm that the electrode is not in the motor tracts)

Stimulation at 50 Hz determines correct electrode positioning (if the tip is correctly positioned, this stimulation will result in pain and a warm or cold sensation on the contralateral side)

RF lesioning is only done once correct sensory testing is obtained with no limb movement on stimulation testing. Multiple lesioning is performed at 75°C, increasing to 85°C. During lesioning, the patient is asked to move the ipsilateral limbs to check no motor lesioning has occurred

The e ect of cordotomy is immediate, with rapid onset of analgesia upon successful lesioning

Complications

Headache

Neuropathic mirror pain can occur on the contralateral side but is commonly mild

A transient Horner's syndrome can be seen, which resolves spontaneously

Respiratory impairment is uncommon with unilateral cordotomy and may be as a result of damage to the reticulospinal tract

Motor weakness (short-term weakness on the ipsilateral side to the lesion is usually self-limiting and due to transient spinal cord oedema)

Urinary dysfunction

Further reading

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20.8 Intrathecal drug delivery systems

Introduction

Intrathecal drug delivery (ITDD) systems provide e ective analgesia with smaller doses of analgesics, thereby reducing medication-related S/Es. There is supportive evidence for the use of ITDD for cancer pain, chronic non-malignant pain (CNMP), and painful spasticity.

(See relevant information in Chapters 6 and 7, and in 13.1 Baclofen, p. 229, 13.8 Clonidine, p. 244, and 29.6 Intrathecal drug delivery treatment for cancer pain, p. 602.)

Indications and e cacy

The polyanalgesic consensus guidelines systematically evaluate the level of evidence and degrees of recommendations for IT therapy. This guideline weighs the risk versus bene ts, outlines best practices, patient selection, and medication selection, and educates about the potential for treatment failure and unacceptable adverse e ects. The main conclusions include:

- Complete assessment and management of a patient's physical, psychological, and social characteristics, and can guide practitioners in determining the appropriateness of initiating, and the e ectiveness of, IT therapy
- The evidence for using IT opioid therapy for cancer pain is 1A. There is strong evidence supporting the use ziconotide for active cancer pain. It has been shown to improve QoL and longevity, with lesser toxic e ects
- There is poor evidence for using IT opioid therapy in CNMP. The National Health Service (NHS) England currently does not routinely commission ITDD for CNMP
- The use of IT baclofen is well established in treating spasticity associated with cerebral palsy, SCI, and MS

Patient selection

Patient selection is extremely crucial and should ideally be done within a multidisciplinary setup

History, physical examination, investigations and psychological evaluation supporting a clear organic pain generator without much psychological overlay

Persistent pain unresponsive to conservative therapy

Intolerable S/Es from systemic opioid therapy

Positive IT trial results

Stable enough medical condition to undergo anaesthesia and surgery

No risk of spinal cord compression—tumour or metastasis

Cognitive ability to use patient device present

Patient education

Risks and bene ts of therapy

Educate on expected signs and symptoms caused by underdosing or overdosing which can be life-threatening

Avoid high-impact activity and scuba diving at a depth of 2 atmospheres

If MRI needed, an IT pump that is MRI-compatible is required. The pump needs to be interrogated after MRI to ensure proper functioning

Contraindications

Absolute

Systemic infection/local infection over insertion site

Clotting abnormalities

Failed IT trial

Allergy to IT drugs used

Relative

Abnormal behaviour/response during screening trial

Types of systems

External pumps

Can be tunnelled or non-tunnelled catheters or with an SC port

Advantages: technically easier, cheaper, suitable for patients with limited life expectancy

Disadvantages: increased risk of infection, cumbersome pumps hampering patient mobility

Implanted pumps

Comfortable for patients and useful for long-term use. Life expectancy should be at least 3 months

Fixed-rate gas-driven pumps:

Flow at constant rate that cannot be changed; only drug concentration can be changed

Advantages: suitable for long-term use, less expensive, have longer re ll intervals

Disadvantages: lack exibility in drug prescription; rate cannot be changed; pump and catheter dead space need to be emptied to stop the pump in an emergency

Programmable pumps:

Battery-driven pump with battery life of 7–10 years

Reservoir volumes usually 20–40 mL

Advantages: o er exibility in changing rate and in using bolus doses

Disadvantages: expensive, re ll intervals usually every 6 weeks, and bolus facility may also mean shorter re ll intervals

Drugs

Cerebrospinal uid dynamics

CSF is secreted by the choroid plexus at 0.3–0.4 mL/hour, with a total volume of 90–150 mL

Current knowledge shows that CSF revolves around the spinal cord in circles with little overall net ow. Instead there is an oscillatory ow determined by HR, BP, and intrathoracic pressure variations

Morphine concentration has a decreasing rostral-to-caudal gradient as the distance from the catheter tip increases. Therefore, the catheter tip needs to be at least at, or just above, the dermatomal level innervating the painful area

Lipophilic drugs remain more localized around the site of intrathecal delivery than hydrophilic drugs which have broader spread in the CSF and can di use cranially into the respiratory centres

Pharmacotherapy of intrathecal analgesia

(See Table 20.8.1.)

Morphine

Acts on mu receptors in the DH and PAG

Only opioid approved by the FDA for IT administration

Small molecule (285 Da) and very hydrophilic substance, resulting in prolonged duration of action

t1/2 in CSF is 80 minutes

300 mg of PO morphine is equivalent to 1 mg of IT morphine

Hydromorphone

Semi-synthetic morphine derivative

Compared to morphine: ve times more potent and lesser supraspinal e ects as it is more lipophilic

Fentanyl

Synthetic anilopiperidine

Highly lipophilic, resulting in segmental analgesia near the catheter tip

Bupivacaine

Amino amide that binds to the subunit of voltage-gated Na^+ channels, reducing Na^+ in ux, thereby inhibiting nerve conduction in sensory bres. Needs close monitoring as motor and autonomic nerve bres are also blocked

Being highly lipid-soluble, its rostral spread in the IT space is limited

Rarely used alone; acts synergistically with opioids, decreasing the need for progressive dose escalation of opioids

Bolus doses of 1–2 mg are more e ective than continuous background infusions

Ziconotide

Also known as SNX-111, it is a novel non-opioid analgesic drug

It is a -conopeptide, derived from the venom of the giant marine snail *Conus magnus*

N-type Ca^{2} channel blocker, acting pre-synaptically; decreases the release of the excitatory NTs SP and CGRP

Completely ionized in the CSF with a high molecular weight of 2659 Da. Therefore, con ned to the CSF, and clearance is by CSF bulk ow, not by metabolism

Can be used for nociceptive and neuropathic pain

No evidence of granuloma formation, developing tolerance, or respiratory depression

Common S/Es: dizziness, confusion, nystagmus, amblyopia, nausea/vomiting, urinary retention

Recommended doses of intrathecal analgesia

IT trial dose	0.1–0.5 mg	0.025–0.1 mg	15–75 mcg	0.5–2.5 mg	5–20 mcg	1–5 mcg	50–100 mcg
Recommended starting daily dose	0.1–0.5 mg	0.01–0.15 mg	25–75 mcg	0.01–4 mg	20–100 mcg	0.5–1.2 mcg (manufacturer suggests up to 2.4 mcg)	50–100 mcg
Maximum concentration	20 mg/mL	15 mg/mL	10 mg/mL	30 mg/mL	1000 mcg/mL	100 mcg/mL	2–3 mg/mL
Suggested maximum daily dose	15 mg	10 mg	1 mg	15–20 mg	600 mcg	19.2 mcg	1.5 mg

Adapted with permission from Deer TR, Pope JE, Hayek SM., *et al.* (2017). The Polyanalgesic Consensus Conference: Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines. *Neuromodulation*, 20: 96–132.

Clonidine

Selective -2 adrenergic receptor agonist
Produces dose-dependent analgesia when delivered intrathecally
Acts at pre-synaptic and post-synaptic DHs, reducing the preganglionic sympathetic ow and decreasing the release of excitatory neuropeptides such as SP and CGRP
FDA-approved for epidural use in cancer pain
Works particularly well for neuropathic pain. Greater e cacy when given intrathecally than systemically
It is not prone to causing granulomas or development of tolerance

Baclofen

FDA-approved for IT use as treatment for spasticity
GABA-B receptor agonist
Decreases spasm-induced pain and can have a primary analgesic e ect mainly in central pain states
Tolerance and tachyphylaxis can occur with long-term infusions
Abrupt withdrawal can be a serious life-threatening situation that mimics a serotonin crisis
Overdose may be a life-threatening situation identi ed by increased drowsiness, hypotonia, seizures, bradycardia, and respiratory depression

Experimental agents

Gabapentin, octreotide, adenosine, XEN2174, AM336

Contraindicated drugs

Ketamine is neurotoxic, causing demyelination and spinal necrosis
Methadone is neurotoxic
Diamorphine breakdown products cause the pump to stall

Polyanalgesic Consensus Conference Algorithm for IT analgesia (2016)

Line 1A Morphine/ziconotide

Line 1B Hydromorphone/morphine + bupivacaine

Line 2 Hydromorphone/morphine + clonidine
Hydromorphone/morphine + ziconotide

Line 3 Hydromorphone/morphine/fentanyl + bupivacaine + clonidine
Ziconotide + bupivacaine
Ziconotide + clonidine

Line 4 Sufentanil + ziconotide
Baclofen
Sufentanil + clonidine

Line 5 Sufentanil + bupivacaine + clonidine
Sufentanil + bupivacaine + ziconotide
Sufentanil + clonidine + ziconotide

Line 6 Opioids + bupivacaine + clonidine + adjuvants
(opioids—all known IT opioids)
(adjuvants—midazolam, octreotide)

Implant technique

Consent

Procedure can be done under part LA and general anaesthesia versus full general anaesthesia with X-ray guidance

Antibiotic prophylaxis as per local policy

Pump side and site need to be marked before the procedure. The pump is usually implanted below the costal margin above the ilium and away from the rectus abdominis

Position initially prone for IT catheter placement and then lateral, or lateral throughout

Sterile preparation and draping

Dural puncture: 15G needle inserted 2–3 vertebral bodies below planned entry to achieve a shallow paramedian entry into IT space. Also ensures catheter stays dorsally

Catheter is inserted with guidewire to the desired level de ned by the area of pain

The guidewire is extracted, and CSF ow at the end of the catheter con rmed. Required length is cut and the end of the catheter clamped after removing the needle. A V-wing connector is used to anchor the catheter. The remaining segment is kept for calculating the priming bolus

Prepare the SC pocket for the pump. This should not be >5 cm deep to ensure interrogation with the patient manager

Pump is lled with the pre-prepared drug under asepsis and xed with sutures

The spinal segment and pump segment are connected via a connector pin that has sutureless squeeze on-and-squeeze o technology. Check for CSF back ow at the pump segment before connecting it to the pump

Programme the pump for background with or without bolus, as decided by the physician

Arrange a date for next re ll, as calculated by the patient manager

Complications

Complications—immediate post-operative period

Bleeding: spinal, epidural, or pocket haematoma

Infection: pump pocket infection or meningitis

Post-dural puncture headache

CSF leak and seroma formation

Complications—hardware problems

Disconnections

Pump stalling, usually secondary to corrosion

Leakage of infused drug

Occlusion, displacement, or kinking of the catheter

Late complications—intrathecal granulomas

Granulomas are in ammatory masses developing at the tip of the catheter

Suspected when there is sudden loss of analgesia and new neurological de cits

More commonly seen with morphine and hydromorphone, and rarely with ziconotide

Diagnosed with help of MRI or CT myelogram

Complications—drug e ects

Opioids:

Nausea/vomiting/pruritus

Respiratory depression

Urinary retention

Endocrine suppression. When used for at least >1 year—monitor testosterone and luteinizing hormone (LH) levels in men, and oestrogen, progesterone, LH, and follicle-stimulating hormone (FSH) levels in women

Bupivacaine:

Sensory/motor de cits

Cardiovascular depression

Clonidine:

Bradycardia and hypotension

Rebound hypertension on withdrawal

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20.9 Percutaneous electrical nerve stimulation

Introduction

Percutaneous electrical nerve stimulation (PENS) is a non-pharmacological neuromodulation therapy for regional neuropathic pain

Indications

Refractory neuropathic pain and a wide variety of conditions (see Table 20.9.1)

Contraindications

Absolute: needle phobia, local or systemic infection, coagulopathy, burns, ulcerations, poorly controlled mental health illness. Not to be applied over the heart, chest wall, and brain

Relative: pregnancy, cardiac pacemaker, epilepsy, anticoagulation, immunosuppression, infants

Mechanism of action

Similar to electro-acupuncture

At 2 Hz stimulation—analgesia is mediated by MOP and DOP receptors

At 100 Hz stimulation—analgesia is mediated by KOP receptors

Reduction in SP and increased release of endogenous corticosteroids, endorphins, and enkephalins

Rebalancing of the mesolimbic loop

Electrical stimulation leading to self-sustaining reverberation and causing resetting of the pain modulation pathways

Indications for percutaneous electrical nerve stimulation

Headache disorders Migraine, tension-type headache, post-traumatic headache	1
Trigeminal neuralgia	–
Peripheral neuropathic pain	
• Sciatica	1
• Diabetic neuropathic pain	1
• Surface hyperalgesia associated with various neuropathic pain (post-herpetic neuralgia)	1
Other chronic pain	
• Chronic neck pain	1
• Chronic low back pain	9
• Osteoarthritis of the hip	1
• Interstitial cystitis (posterior tibial nerve stimulation)	–
• Chronic pelvic pain	–
• Class IIIB chronic prostatitis/chronic pelvic pain (posterior tibial nerve stimulation)	1

RCT, randomized controlled trial.

Source: data from Interventional procedures guidance [IPG450]. London, United Kingdom: National Institute of Clinical Excellence.

Technique

Acupuncture needles (32–36G) or PENS needles

Single-lead probe with grounding pad or ne-gauge needle probes

Asepsis

Insertion of needle in fatty tissue under the skin, close to the relevant nerve or the regional distribution of the pain

Needles are connected to a low-voltage pulse generator

Electric current passed through the needles

Alternating frequency: 15/30 Hz (e ective for 58%) have been found more e ective than 4 or 100 Hz (49%)

Stimulation duration: between 15 and 60 minutes (30 minutes were more e ective than 15 minutes and nearly equally as e ective as 45 minutes)

Montage providing stimulation along the involved nerve root is better than di use placement

Recommended 3-weekly sessions of 30 minutes for 2 weeks

Sensations perceived: paraesthesiae and/or muscle twitch or contractions in the stimulated myotome

Complications

NICE did not demonstrate any adverse events, but evidence on safety is limited

Potential adverse events: bleeding, local bruising, swelling and haematoma, flare-up of pain, neurovascular damage, local nerve damage, pneumothorax (over chest wall), cardiac tamponade (over heart), dislodgement (with loss of effect), unpleasant paraesthesiae

Advantages of percutaneous electrical nerve stimulation versus transcutaneous electrical nerve stimulation

Reduction in pain
Reduction in oral analgesic medication requirement
Improved physical activity, sleep, and QoL
Satisfaction with treatment

Further reading

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20.10 Peripheral nerve stimulation

Definition

Use of electrical stimulation along peripheral nerves as a neuromodulatory technique to deliver pain relief

Application

To treat persistent pain that has failed conservative therapy
There are specific devices, including those using wireless technology
Many techniques and targets are under extensive investigations to treat a wide range of conditions
Success of peripheral nerve stimulation (PNS) depends upon patient selection, method used, selection of electrodes, placement of batteries, surgeon's experience, and identification of targets
US-guided percutaneous approaches are simple, easy to use, and widely applicable for many neuropathic pain problems

History

Use of PNS began in the mid 1960s (earlier than spinal cord stimulators)
Originally the technology was the same as that of spinal cord stimulators
The first percutaneous PNS was reported in 1999
Becoming more popular recently due to developments in ultrasound-guided pain interventions and technology advancements in electrical leads and wireless technology

Descriptions of PNS

External peripheral nerve stimulation (EN-PNS)
Internal peripheral nerve stimulation (IN-PNS)
There is an overlap of described terminologies and how the stimulation is applied

Types of PNS

Transcutaneous electrical nerve stimulation (TENS)
Percutaneous electrical nerve stimulation (PENS)
Peripheral nerve eld stimulation (PNFS)
Subcutaneous peripheral nerve stimulation (SENS)

Indications/conditions treated using PNS

Any peripheral nerve entrapment or neuropathy that is accessible for implantation could be treated with PNS
Neuropathic pain (all types, including persistent post-surgical neuropathic pain, entrapment symptoms, CRPS, post-infection, and post-chemo-/radiotherapy)
Visceral pain
Abdominal pain
Back pain
Cardiac pain
Epilepsy
Facial pain
Headache
Incontinence
Obesity

Conditions treated—targets/areas

This is an expanding area; many research projects are ongoing, and new targets identi ed
Headache, occipital neuralgia—occipital nerve stimulation (ONS) and sphenopalatine ganglion stimulation
Trigeminal neuralgia (trigeminal nerve branches stimulation)
Migraines—vagus nerve stimulation (VNS) (ongoing trials for epilepsy and depression)
Obesity—gastric stimulation
Brachial plexus injury—brachial plexus stimulation
Upper limb neuropathic pain—radial, median, or ulnar nerve stimulation
Shoulder pain—suprascapular nerve, axillary nerve, deltoid muscle (IM stimulation)
Thoracic wall pain—paravertebral plexus stimulation
Intercostal neuralgia—intercostal nerve stimulation
Post-hernia repair pain—ilio-inguinal/ilio-hypogastric nerve, genitofemoral nerve stimulation
Post-surgical scar pain—cutaneous nerve stimulation
Post-radiotherapy pain—cutaneous nerve stimulation
Low back pain—percutaneous stimulation, medial branches stimulation, cluneal nerve stimulation
Chronic pancreatitis pain—splanchnic nerve
Stump pain after amputation—cu electrodes/speci c nerve stimulation
Percutaneous posterior tibial nerve stimulation (PTNS) for urinary incontinence (overactive bladder)
Pudendal nerve
Sacral stimulation—pelvic pain, urinary incontinence, faecal incontinence
Peripheral nerves of upper and lower limbs—plexus and individual nerves
Patchy area of neuropathic pain anywhere in the skin of most of the body area (PENS)

Techniques

Either landmark, nerve stimulator, or US-guided techniques are used

The leads are placed percutaneously or surgically (open)

Some centres do a trial period similar to spinal cord stimulation (SCS)

Complications

Mainly related to hardware

The most common hardware-related complication is lead migration; the largest case series of PNS showed 2–13% of PNFS leads were a ected

Biological complications include infection or pain over implant site

Serious complications, such as neurological damage, have not been reported

Current evidence

Most RCTs currently available are on sacral stimulators (seven RCTs) and ONS (one RCT)

Other studies—mostly retrospective analyses, case series, anecdotal reports, and small studies

Future

There will be further developments in technology (especially leads and batteries speci cally designed for PNS)

Use of US for identifying and targeting peripheral nerves will widen the application of PNS

More evidence is required (RCTs and multicentre studies)

Further reading

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20.11 Spinal cord stimulation

Introduction

Spinal cord stimulation (SCS) is an interventional pain procedure that involves placement of electrodes in the posterior epidural space to stimulate components of the spinal cord to relieve pain

Currently reserved for treatment of refractory neuropathic pain and pain of ischaemic origin

Unlike most medical procedures, it is possible to perform a temporary trial of therapy (e.g. for 7–10 days) before committing to permanent implantation

It has the advantage of reversibility and safety

Mode of action

Initially based on Wall and Melzack's gate control theory of pain

- The electrodes emit an electric eld that stimulates the dorsal column of the spinal cord at frequencies typically between 40 and 70 Hz (higher frequencies are also available)
- This activates A a erents that produce pleasant paraesthesiae over speci c anatomical areas
- Overlapping the painful areas with this paraesthesiae produces analgesia as A stimulation inhibits A-delta or C- bre transmission

Although the gate control theory is a useful concept, the exact mechanism of action has not been fully elucidated and its mechanism of action is likely to involve:

- Ortho- and anti-dromic activation of sensory a erents
- Modulation of DH cells and WDR neurons at the spinal cord
- Activation of GABA transmission
- Activation of higher inhibitory pathways

Indications

SCS is primarily e ective for pain of neuropathic origin

Some evidence of its e cacy in pain of ischaemic origin exists

Nociceptive pain is not a ected by SCS

SCS is commonly used in:

- Lumbar radicular pain as a result of previous spinal surgery
- CRPS
- Chronic post-surgical neuropathic pain

Contraindications

Pain that is predominantly nociceptive

Allergies to certain metals (most of the devices include metallic parts)

Signi cant psychosocial comorbidity

Widespread chronic pain syndromes

Central pain syndromes

Insu cient cognitive function to use and self-adjust stimulation

Electrode placement

Success of SCS is determined by stimulation of dorsal column nerves to produce overlapping paraesthesiae

Correct electrode placement is critical to its success (see Table 20.11.1)

Electrode placement

Neck and arm	C2–5
Chest	C7–T1
Low back	T7–9
Legs	T9–12

Patient preparation and electrode positioning

Strict aseptic technique is mandatory

Image guidance using uoroscopy is essential

Electrode placement depends on the anatomical area of pain

This procedure is done under LA and/or sedation, as intraoperative stimulation is performed to ensure correct placement of the electrode(s) unless high-frequency stimulation is used

Types of electrodes

Cylindrical electrodes can be used for both trial and permanent implants

Surgical paddle electrodes are only for permanent implants (lower power consumption and less migration, but a laminotomy is required for insertion and removal is technically more di cult)

Temporary percutaneous trial

Placement of the lead percutaneously under image guidance:

- Patient in prone position
- A 14G modi ed Tuohy needle is used to access the epidural space using a loss of resistance technique (the Tuohy needle is placed at a shallow angle, and skin entry is usually two vertebral levels below the desired area for loss of resistance)
- Once the epidural space is accessed, a cylindrical electrode is inserted and steered under uoroscopic guidance to the desired anatomical area
- The patient is then woken up, and intraoperative activation of the electrode is performed to ensure correct coverage unless high frequency is used

A second electrode can be placed if further anatomical areas are needed to be stimulated

The electrode is left *in situ* and anchored to the skin with a suture

The trial period is typically 7–10 days and the patient can then determine both the analgesic e ect of spinal stimulation and its tolerability

Full permanent implant

An incision over the back is made prior to placement of the electrode in the epidural space (as described earlier)

This allows the electrode and connector to be implanted under the SC tissue

A battery is placed in the buttock area or loin

Intraoperative testing is performed (as described earlier)

Complications

Although minor complications are common, major or serious complications are rare (see Table 20.11.2).

Common complications of spinal cord stimulation

Hardware-related	
Electrode migration	13.4%
Electrode damage *in situ*	9.1%
Battery failure	1.6%
Battery-related discomfort	6%
Infection	3.4%

Electrode migration can frequently be compensated for by reprogramming and/or using an alternative electrode con guration

Infections require removal of the system and the use of systemic antibiotics

Most of the current systems used are now MRI-compatible and newer devices are available that are safe to use at up to 1.5 Tesla

Post-procedure management

Patients are encouraged to restrict excessive spinal movements for 3 months to minimize the risk of electrode migration (a small degree of electrode migration can be compensated for by reprogramming the stimulation)

Non-rechargeable batteries can last for 5–6 years, depending on how much stimulation is used

Rechargeable batteries have the advantage of being smaller and able to accommodate higher energy requirements, but they will require changing every 8–10 years

The procedure to change the battery is straightforward and done as a day case

If the patient needs an MRI scan, check if the implanted device is MRI-safe

Special points

The most important factor associated with success is careful patient selection

It is important that patients undergoing this procedure understand that stimulation only works as part of a pain management approach and be aware of the biopsychosocial factors that a ect chronic pain

Newer modalities of stimulation have the potential to expand on both the indications for use and treating areas of pain that were previously di cult

Newer modalities of stimulation

High-frequency and burst stimulation (these are paraesthesiae-free systems and can target axial back pain better than conventional systems; another advantage is that intraoperative testing is not required and the electrode is placed anatomically)

DRG stimulation (this can improve stimulation in more localized areas such as the foot)

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20.12 Transcutaneous electrical nerve stimulation

Background

De ned as 'the application of electrical stimulation to the skin for pain control'

Accepted by the medical community following the publication in 1967 of a paper which showed a reduction in neuropathic pain in eight patients who were stimulated at 100 Hz with an intensity su cient to stimulate large a erent bres
Inexpensive
Non-invasive
Easy and safe to use
Clinical evidence of e ectiveness controversial

Mechanism of action (several theories)

Gate control theory
Interruption of the transmission of noxious signals through stimulation proximal to the injury site, resulting in anti-dromic conduction along the nerve
Production and release of endogenous opioids in the PAG area and reticular activating system

Components

Device with internal electronics that allow variable programming
Dials on the device to allow selection of the intensity for each channel, pulse duration, and frequency and pattern of stimulation
Connecting wires
Two or four electrodes/pads

Method of application

Application site

Over healthy skin (not broken)
Close to the painful area
Within the same myotome, dermatome, or sclerotome
Choose acupuncture points, trigger points, or over the peripheral nerve in neuropathic pain
Close to the spinal nerves next to the vertebral column
When not feasible or accessible, opt for the corresponding position on the contralateral side

Avoid application over

Front of the neck near the carotid sinus (precipitation of arrhythmias)
Skin without cutaneous sensation
Pharyngeal area (it could theoretically a ect breathing)
Pregnant uterus

Contraindications

Pacemakers and implantable de brillators
Epilepsy
Arrhythmias
Over malignancy
Over broken skin
Over metalwork

Stimulation patterns of TENS

Employed	Standard	Acupuncture-like TENS (ALTENS)
Onset	Immediate	Delayed for hours or days
Presumed mode of action	Stimulation of large A-beta bres: Gate mechanism Anti-dromic conduction Release of dynorphin at the dorsal horn	Release of -endorphins at the dorsal horn through stimulation of high-threshold A-delta and C- bres
Duration of action	Short	Prolonged
Other types		
Modulation TENS	Automatic variation of pulse width, frequency, and duration	Dual bene t of both conventional and ALTENS
Burst TENS	Bursts of conventional, high-frequency stimulation of increasing intensity	Useful, especially over prolonged use, due to prevention of adaptation of nerve bres

Clinical use

(See Table 20.12.1.)

Has been used for decades in various chronic pain conditions, primarily low back pain, and in acute pain such as labour

E ectiveness remains controversial in view of the relative paucity of evidence from high-quality, rigorously conducted RCTs until recently

Currently, it is used as part of a multimodal approach in an attempt to reduce use of other analgesia in the following.

Acute pain

Labour pain: the electrodes are applied over the spinal nerve roots of T10–L1 and S2–S4, using either conventional or burst modes

Acute post-operative pain: application of sterile electrodes parallel to the incision, in addition to possible occasional application close to the corresponding spinal segments

Chronic pain

Knee OA: using both conventional TENS (incl. conductive silver garments for the knee, elbow, hands, and feet) and acupuncture like TENS

Primary dysmenorrhoea: electrodes applied either to the abdomen or close to thoracic segments that receive input from nociception in the uterus (occasionally, they have been placed on classical acupuncture points)

Neuropathic pain

Post-stroke shoulder pain: based on anecdotal case reports

Although it had been traditionally used for chronic low back pain, current guidance in UK advises **against** its use for this indication

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CHAPTER 21

Surgical Techniques

Erlick Pereira

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21.1 Spinal decompressive surgery

Anatomy

The spinal cord travels in the spinal canal from C1 to L1 vertebrae where it becomes the conus medullaris, then the theca containing the cauda equina of lumbo-sacral nerves from L2 to S4

Nerves can be trapped in lateral recesses of the spinal canal or foramina by stenosis from ligamentum avum hypertrophy, bony osteophytes, or disc prolapses. Postero-lateral disc prolapses compress traversing nerves, and lateral disc prolapses compress exiting nerves

Cervical nerves exit at the foramina above the vertebral level (e.g. C7 nerve at C6–7). Thoracic and lumbar nerves exit below the vertebral level (e.g. a far lateral L2–3 disc prolapse will compress the exiting L2 nerve root)

Indications

Pain, weakness, altered sensation, loss of function causing signi cant disability and impairment of QoL, persisting for >3 months with focal neural compression unrelieved by analgesia ± injections

Cervical myelopathy (cord compression from canal stenosis)—anterior cervical discectomy and fusion if 1–2 levels, cervical laminectomy ± fusion if 3 levels

Cervical radiculopathy (nerve compression)—cervical foraminotomy if foraminal stenosis, anterior cervical discectomy, and fusion if vertebral osteophytes and disc prolapse

Thoracic myelopathy—thoracic laminectomy if canal stenosis or thoracotomy and discectomy if central disc prolapse

Neurogenic claudication—lumbar laminectomy

Sciatica—lumbar discectomy if disc prolapse, foraminotomy if foraminal stenosis, undercutting facetectomy if lateral recess stenosis (not always possible without fusion)

Contraindications

Deformity (scoliosis, kyphosis, spondylolisthesis) requiring fusion

Coagulopathy (anticoagulation should be reversed/stopped before surgery)

Un t for general anaesthesia (cardiovascular, renal, pulmonary impairment)

Multiple past spinal surgeries (may require fusion or spinal cord stimulation)

Trauma, malignancy (may require xation)

Technique

Most decompressions are open midline longitudinal incisions, with the paravertebral muscles stripped to expose the posterior spine. Anterior cervical decompressions are approached in a plane of deep investing cervical fascia between the sternocleidomastoid and the carotid sheath laterally and the oesophagus, trachea, and recurrent laryngeal nerve medially

Radiographs before and during decompression mandatory to con rm the spinal level decompressed

Complications

Infection (1%)

Bleeding requiring blood transfusion (1%)

Paralysis or focal weakness and loss of function (0.1%)

CSF leak and potential meningitis (1%)

Recurrent disc prolapse/stenosis

Adjacent level disc prolapse/stenosis

For anterior cervical approach—injury to oesophagus, trachea, recurrent laryngeal nerve (di culty with speaking, breathing, or swallowing), stroke

General anaesthetic risks (deep vein thrombosis (DVT), pulmonary embolus (PE), pneumonia, stroke, death)

Special points

Open approach is standard of care. X-ray-guided percutaneous decompressions are less reliable. Microscopes and, more rarely, loupes and endoscopes are used to improve visualization of neural compression

Most surgery has post-operative wound pain for several days and necessitates overnight hospital stay

Most surgeons advocate a wound drain for a day after surgery and 2 days of bed rest if CSF leak occurs at surgery

Best outcomes arise from focal nerve root compression that is anatomically consistent with the dermatomal pain, with >80% of patients improving. In contrast, the aim of surgery in myelopathy is to prevent symptom progression

Early discectomy for sciatica promotes early mobilization, but 1-year outcomes are similar to conservatively managed sciatica

Further reading

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21.2 Spinal fusion surgery

Introduction

Spinal stability is conferred by ligaments, bones, and intervertebral discs. Movement or damage to any of these elements can result in pain, deformity, or loss of function

Spinal fusion surgery fuses two or more vertebral bodies to correct abnormal spinal movement as a cause of pain, remove the intervertebral disc (the presumed pain generator), and provide spinal stability. Best outcomes are normally found when:

- History, examination, and investigations suggest that the pain generator is most likely a single intervertebral disc
- Patients are motivated and fit, with realistic expectations, who understand the surgical risks
- Patients have no profound dysfunctional lives or severe pain-related disabilities

Spinal fusions can be combined with neural decompression surgery (e.g. discectomy, laminectomy) when neural compression is also a pain generator

Patients who have had a spinal fusion can develop degenerative changes in adjacent spinal vertebrae due to changes in spinal mechanics from the surgery

Surgical techniques

Spinal fusions involve placing a bone graft between adjacent vertebrae

There are multiple techniques and different hardware that can be used to provide spinal stability (cages, screws, plates) until the bone graft heals

Posterior interbody fusion

A lateral mass screw is inserted in the cervical spine

A pedicle screw is inserted in the thoracic, lumbar, or sacral spine

A lateral gutter bone graft or bone substitute is inserted

Lumbar spine posterior interbody fusion

Intervertebral disc is replaced with a titanium or polyethyletherketone cage and bone graft/substitute

Commonly performed posteriorly or transforaminally through open or minimally invasive approaches

Anterior lumbar and extreme lateral interbody fusion

Confers the advantages of implanting cages that cover a greater surface area of the vertebral body endplates, thus creating a stronger construct. This may effectively restore lordosis or correct scoliosis, and indirectly decompress neural elements

Stability may be augmented by an overlying plate and pedicle screws

Anterior cervical discectomy and fusion

Can be stand-alone or augmented by a plate if over multiple levels

Can directly decompress neural elements

Cervical corpectomy

Indicated for vertebral body disease/neural compression

Preformed with a cage and plate or a bular/iliac crest strut graft

Transcervical odontoid screw, posterior C1–2, or occipito-cervical fusion

Indicated for cranio-cervical junction pathologies

Indications

Spondylolisthesis

Multi-level cervical canal stenosis

Degenerative disc disease with vertebral body Modic changes and positive discography

Deformity (kyphosis, scoliosis)

Trauma (often xed, rather than fusion, as screws can be removed after fracture union)

Metastatic spinal cord compression

Other causes of spinal instability (e.g. spondylodiscitis, osteomyelitis, chordoma or other tumour, osteoporotic collapse, RA at cranio-cervical junction)

Contraindications

Osteoporosis, osteopenia

Coagulopathy

Some metal allergies

Deformity is a contraindication to short spinal segment fusions, as longer constructs respecting sagittal and coronal balance should be considered by trained deformity surgeons

Paraspinal myopathies and movement disorders (e.g. Parkinson's disease, dystonia) require caution as outcomes are often worse

Technique

Extreme care with infection control. Vancomycin powder is commonly used in wounds

Usually open midline incisions. Small ank or larger thoraco-abdominal incision for extreme lateral interbody fusions. Mini-laparotomy or Pfannenstiel incision in the abdomen for an anterior lumbar fusion. Transverse anterior neck incision for an anterior cervical discectomy and fusions

Can be minimally invasive or image-guided by intraoperative CT, which reduces surgeon intraoperative radiation exposure and can reduce screw misplacement risk

Complications

Standard risks of spinal surgery: paralysis, focal weakness, pain or numbness from nerve injury, CSF leak, meningitis, infection, and bleeding

Instrumented fusion confers additional risks of screw misplacement, cage misplacement or migration, non-union, adjacent spinal segment failure, and instrumentation failure

Anterior and extreme lateral interbody fusions have speci c risks related to their approaches, both including aortic, iliac vessel, or inferior vena cava injury

Speci c complications include:

- Lateral interbody fusions: lumbo-sacral plexopathy
- Anterior lumbar fusion: ureteric damage, hypogastric plexus injury resulting in retrograde ejaculation or vaginal dryness

Special points

Lumbar fusion for back pain in degenerative disc disease without spondylolisthesis is controversial with little strong RCT evidence and preliminary data suggesting such patients if otherwise refractory may bene t from non-surgical treatment strategies

Further reading

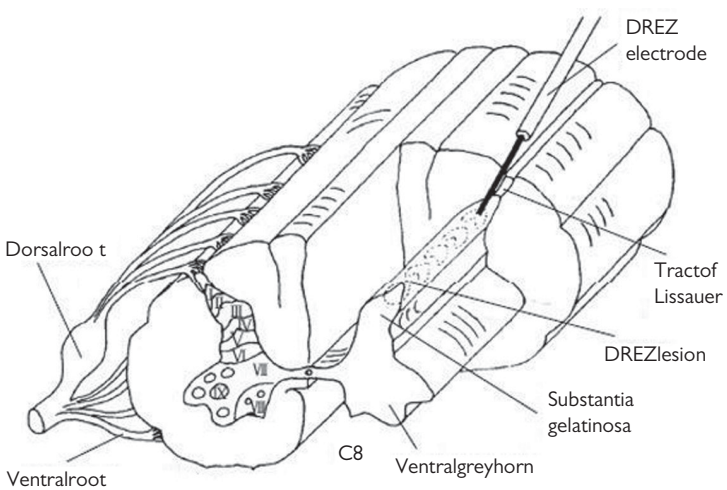
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21.3 Dorsal root entry zone lesioning

Introduction

The dorsal root entry zone is a region comprising the central portion of the dorsal rootlet, the medial part of Lissauer's tract, and the rst ve layers of Rexed's laminae in the dorsal horn where the a erent bres synapse (see Fig. 21.3.1)

Each dorsal root divides into 4–10 rootlets, each 0.25–1.5 mm in diameter and each with a peripheral and a central segment. The transitional zone between the two segments is at the pial ring approximately 1 mm outside where the root penetrates the dorsolateral sulcus. Fine pain bre group in the lateral dorsal root entry zone, and large tactile bre group medially towards the dorsal columns



Anatomy of the dorsal root entry zone (DREZ)

Indications

Dea erentation pain after nerve root avulsion
Brachial plexus avulsion
SCI restricted to a few dermatomes
PHN
Amputation pain (phantom limb or stump)

Contraindications

Coagulopathy
Whole or hemi-body pain
Non-dermatomal SCI pain

Technique

Prone patient
Laminectomies over a ected nerve roots
Dural opening longitudinal and paramedian over a ected nerve roots and microscopic identi cation of dorsal root entry zone by viewing intact rootlets above and below the injured area
RF thermocoagulation at 80°C for 15 seconds (Nashold technique) or sharp microincision (Sindou technique) ipsilateral to avulsed nerve roots from caudal to superior intact rootlet to rostral to inferior intact rootlet if over several segments; 30–45° angulation of implement and depth of 2–3 mm. In paraplegic patients, it can be combined with a cordotomy
Standard dural closure with 2 days of bed rest after surgery

Complications

Ipsilateral weakness (transient 10%, permanent 5%)
Ipsilateral loss of proprioception (transient 10%, permanent 5%)
Usual risks of intradural spinal surgery (infection, bleeding, pain, CSF leak, meningitis)

Special points

Best outcomes from brachial plexus avulsion (>80% long-term signi cant improvement) and SCI with limited dermatomal involvement
Destructive surgery, so neuromodulation (e.g. deep brain stimulation (DBS), spinal cord or DRG stimulation) may be favoured as rst-line therapy

Further reading

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21.4 Deep brain stimulation

Introduction

Spinothalamic pain processing tracts in the spinal cord are modulated in the midbrain periaqueductal grey (PAG) and the sensory thalamus en route to cortical pain processing brain areas such as the insula and anterior cingulate cortex

Midbrain PAG (see Fig. 21.4.1) is superior and anterior to the superior colliculi (thus, deep electrode stimulation can cause oscillopia), and posterior to the red nuclei and reticular thalamus. It has a rostrocaudally inverted homunculus, with the face represented most caudally and the legs most rostrally

The sensory thalamus consists of the ventral posterior medial and lateral nuclei, 6–14 mm lateral to the posterior commissure. The ventral posterior thalamus has a mediolaterally oriented somato-sensory homunculus, with the face represented in the ventral postero-medial and the legs in the ventral postero-lateral thalamus

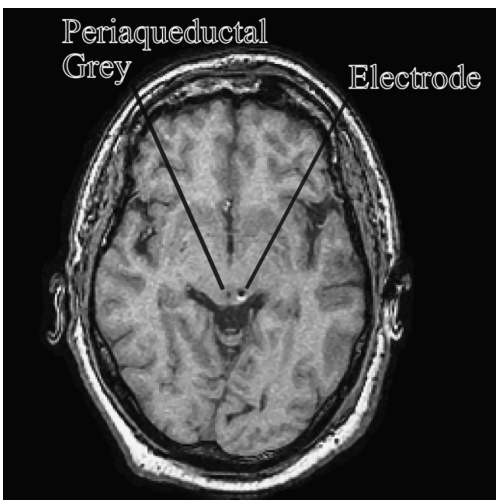
The anterior cingulate cortex is involved in emotional and pain valency processing. Its rostral, supragenual component is a target for DBS

Entry points for DBS surgery are usually frontal and anterior to the coronal suture, to avoid passing through the primary motor cortex more posteriorly, and ipsilateral and extra-ventricular to minimize the bleeding risk and inaccuracy

Indications

Refractory pain not responding to conventional treatments from the following:

- Post-stroke pain (also amenable to motor cortex stimulation)
- Cranial/facial pain (e.g. post-craniotomy or anaesthesia dolorosa)
- Post-amputation (phantom limb or stump) pain



Deep brain stimulation electrode placement

Brachial plexus avulsion
SCI
Low back pain refractory to spinal cord stimulation and spinal surgery
Hemi- or whole-body neuropathic pain
Trigeminal autonomic cephalgia (the posterior hypothalamus is the target)

Contraindications

Coagulopathy
Hydrocephalus
Dementia
Functional pain syndromes

Technique

Awake surgery desirable to assess intraoperative response to DBS
Stereotactic frame placed on the head and used to calculate the coordinates of the brain target
Brain targets include contralateral ventral posterior thalamus (medial—face, lateral body), contralateral midbrain PAG (see Fig. 21.4.1), and bilateral rACC (for hemi- or whole-body pain)
After awake electrode placement and subsequent CT brain con rming correct placement of the electrodes, the stereotactic head ring is removed and wires externalized for a week of trialling
If trialling successful, then brain electrode wires are tunnelled to a subclavicular implanted pulse generator under general anaesthesia

Complications

Risks of brain surgery, including infection, bleeding causing stroke or death, and seizures (higher risk with anterior cingulate DBS)
Chest area site with implanted pacemaker—highest risk of infection (2%)
Electrode malposition requiring revision surgery
Implanted hardware failure or breakage
Stimulation S/Es (e.g. twitching, visual problems, unpleasant sensation)

Special points

Safer forms of neuromodulation (e.g. DRG stimulation for amputation pain, ONS for cluster headache) can be trialled before DBS
No strong RCT evidence. Large case series suggest initial 80% e cacy, dropping to two-thirds at 2 years and to 50% at half a decade

Further reading

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CHAPTER 22

Miscellaneous Interventions

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22.1 Bier's block

Introduction

Bier's block is a peripheral IV regional technique that may be used for chronic pain management of the limbs

Evidence to support its e cacy is limited

Anatomy

Arteries and peripheral veins of the limbs

Indications

CRPS

Ischaemic limb pain

Neuropathic limb pain

Contraindications

Patient refusal

Allergy to LA

Cannulation site infection

Crush injuries

Compound fractures

Arterio-venous shunt or stula

Severe peripheral vascular disease

Disrupted venous drainage of the limb

Di cult venous access

Severe liver disease

Sickle cell disease

Patient preparation and positioning

Supine with standard monitoring

IV access established away from limb to be blocked

Ensure tourniquet is functional and checked for air leaks

Technique

Place a double-cu ed pneumatic tourniquet on the block limb over a stockinette bandage

Cannulate the most distal vein possible in the block limb

Elevate the limb above the level of the heart for 1–2 minutes for passive exsanguination

Apply a compression bandage to the elevated limb spirally up to the tourniquet cu

Occlude the artery proximal to the tourniquet; in ate the distal cu of the tourniquet to 50–100 mmHg above systolic BP, then in ate the proximal cu . Once the proximal cu is in ated, de ate the distal cu and remove the compression bandage

Slowly inject LA into the IV cannula in the block limb—typical volume of 40–60 mL of 0.5% lidocaine (up to 3 mg/kg) or 0.5% prilocaine (up to 6 mg/kg)

Onset of anaesthesia takes up to 5 minutes. Progressive numbness and limb insensitivity, followed by motor paralysis and skin discoloration

The distal tourniquet is in ated and the proximal one de ated when tourniquet pain occurs (usually 30–45 minutes)—allowing 15–20 minutes of tourniquet tolerance

Gradually release the tourniquet in two steps at the end of the procedure

Complications

Complications are rare and often due to equipment malfunction or not following the correct procedure for performing the block

LA toxicity—often from equipment failure/poor tourniquet in ation

Haematoma at cannula site

Engorgement of the limb—more common in patients with arteriosclerosis

Ecchymosis/SC haemorrhage

Tourniquet complications

Special points

Exact mechanism of action is subject to debate. LA is thought to di use to nerve trunks, peripheral nerves, and nerve endings. Nerve bre compression and ischaemia from the tourniquet may also contribute to the block

The following can be added, which may improve the e cacy of Bier's blocks:

- Mg^{2} —possible direct analgesic e ect, NO release, and Ca^{2} channel and NMDA receptor blockade
- -2 adrenoreceptor agonists—likely decrease in AP conduction along A-delta and C-bres and hyperpolarization of cation channels
- NSAIDs (e.g. ketorolac)—e ect on PGE2 and PGI2 release may be of relevance in CRPS, along with reduction in in ammation
- Corticosteroids—attenuation of in ammation in CRPS (also may prolong LA action)
- Ketamine—NMDA antagonism
- Ondansetron—serotonergic nociceptive pathways, action on Na^{+} channels

Further reading

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2. New York School of Regional Anaesthesia. Intravenous regional block for upper and lower extremity surgery. https://www.nysora.com/techniques/intravenous-regional-anesthesia/intravenous-regional-block-upper-lower-extremity-surgery

22.2 Bursa injection

Introduction

Bursitis is in ammation of uid- lled sacs which are normally positioned between two muscles or between a muscle and its tendon or bone

Bursa injections can be performed in patients with bursitis who fail to respond to conservative therapy. Evidence to support its e cacy is limited

Contraindicated if there is an infected bursa (needs aspiration and antibiotics)

Bursa injections are normally done with LA (e.g. 5 mL of 0.5% bupivacaine) and steroid (e.g. 40 mg triamcinolone)

Refer to Chapter 15 on overview of interventions in Section 4 for standard clinical practice before, during, and after interventions in pain management

Subacromial bursa injection

Anatomy

Subacromial space noted to be above the supraspinatus muscle and below the acromion

Bursa extends from the subdeltoid to the subacromial space

It is the largest bursa in the body (up to 20 mL of uid)

Indications

Subacute and chronic shoulder pain from subacromial bursitis

Technique

Sitting position and shoulder in neutral position

Linear transducer placed over the distal acromion in a perpendicular position

Important to obtain a 'bird's beak view' of the supraspinatus tendon

Needle is inserted in an in-plane orientation into the thin, double hyperechoic capsule. May be enlarged in bursitis

Inject LA and steroid under direct vision to avoid disruption of the supraspinatus tendon

Special points

Aim bevel away from the supraspinatus—avoid damaging the tendon

Double-lined capsule may be seen as a uid- lled sac

Slight anterior orientation may deliver a better view

Greater trochanter bursa injection

(See 23.14. Greater trochanteric pain syndrome, p. 477.)

Anatomy

The greater trochanter bursa is situated over the most prominent and lateral part of the hip at the insertion of the gluteus muscles

Symptoms include pain along the outer surface of the leg/hip towards the knee

Indications

Acute or chronic in ammation of the greater trochanter bursa due to OA, RA, repetitive use, trauma, or other causes

Ultrasound-guided injection

Linear probe

Lateral position with the hip gently exed

Imaging of the greater trochanter in a transverse plane (short axis)

Approach from a posterior to anterior position in plane with the transducer

LA and steroid injected within the peritendinous soft tissues of the greater trochanter

Fluoroscopic-guided injection

Supine position with the knees straightened

Locate the greater trochanter and the point of maximal tenderness in AP view

Needle inserted perpendicular to the skin

Pass down directly onto bone contact and then withdraw before injecting

Inject LA with steroid

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22.3 Ilio-inguinal nerve, ilio-hypogastric nerve, and genitofemoral nerve block

Anatomy of the ilio-inguinal nerve (IIN) and ilio-hypogastric nerve (IHN)

The IIN and IHN arise from the anterior rami of L1, with contribution from T12

Both nerves run between the lateral border of the psoas major muscle and the quadratus lumborum muscle

Above the iliac crest, both nerves pierce the TA muscle and continue anteriorly, medial to the ASIS

The IHN pierces the IO muscle medial to the ASIS, and then travels between the IO and the EO muscles

One inch above the super cial inguinal ring, the IHN pierces the aponeurosis of the EO muscle

The IIN nerve runs parallel to and below the IHN, and it pierces the lower border of the IO muscle and passes between the crura of the super cial inguinal ring in front of the spermatic cord

The IHN nerve provides sensory bres to the skin over the lower part of the RA muscle (ipsilateral to the midline) and above the inguinal ligament (see Fig. 23.3.1)

The IIN supplies the skin over the supero-medial area of the thigh and the skin over the root of the penis and anterior scrotum (in women: mons pubis and labia majora)

Anatomy of the genitofemoral nerve (GFN)

It originates from the L1 and L2 nerve roots

At the level of the L3–4 intervertebral disc, it pierces the psoas muscle

On the anterior surface of the psoas muscle, it either runs as a single trunk or as separate genital and femoral branches

The femoral branch follows the external iliac artery and passes with it under the inguinal ligament. It supplies the skin overlying the femoral triangle

The genital branch passes through the internal inguinal ring of the transversalis fascia and continues in the inguinal canal

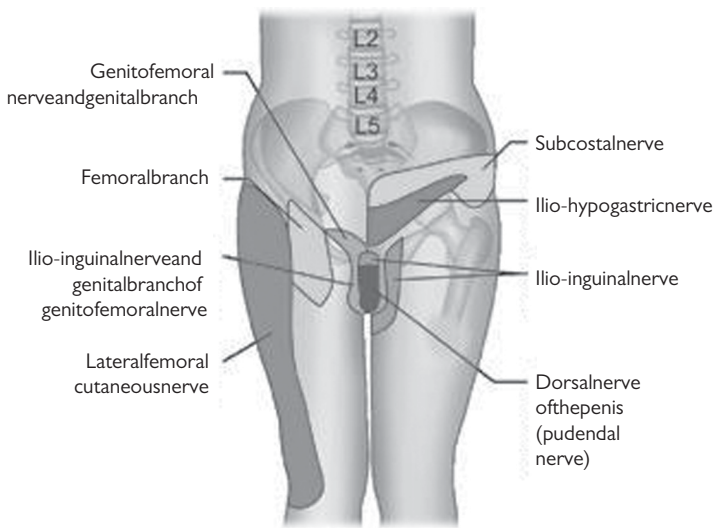
The GFN runs either outside the spermatic cord or in ventral, dorsal, and inferior locations or within the cremaster muscle

The genital branch supplies the cremaster muscle and the anterior scrotal skin in males, and the skin of the mons pubis and labia majora in females (see Fig. 23.3.1)

Indications

Chronic post-surgical pain—after hernia repair, Caesarean section, laparoscopy, and lower abdominal surgery

Post-vasectomy pain



Territory of supply of the ilio-inguinal, ilio-hypogastric, and genitofemoral nerves

Reproduced with permission from Thomas, P, and Das, G. (2015). The diagnostic dilemma of a genitofemoral-ilioinguinal overlap syndrome, *Journal on Recent Advances in Pain*, 1(1): 28–30. DOI: 10.5005/jp-journals-10046-0009

Genitofemoral neuralgia
Chronic testicular pain

Contraindications

Patient refusal
Localized infection
Allergy to LA and steroids

Patient preparation and positioning

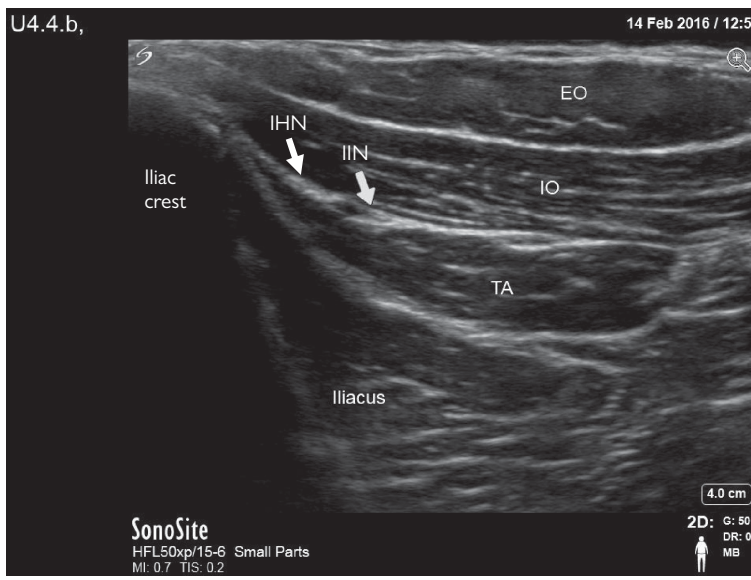
Patient in supine position
Equipment: linear US probe (6–13 MHZ)

Complications

Failure
Infection, bleeding, bruising
Injury to bowel
Nerve injury and persistent pain

Technique for IIN and IHN block

The US probe is positioned 3–4 cm cephalad and lateral (posterior) to the ASIS, perpendicular to the inguinal line joining the ASIS and the pubic tubercle, with the lateral end of the probe just above/posterior to the ASIS. The probe is then tilted until all three layers of muscles (TA, IO, and EO) are visualized (see Fig. 22.3.2)



Ultrasound image of the ilioinguinal (IIN) and iliohyogastric (IHN) nerve block (arrows). EO, external oblique muscle; IO, internal obliques muscle; TA, transverse abdominis muscle; Iliacus, iliacus muscle

Reproduced with permission of Andrzej Krol, St. George's Hospital London

Splitting of the fascial layer between the IO and TA muscle is observed and targeted. Both nerves can run together or approximately 1 cm apart. Colour Doppler is used to locate the deep circum ex iliac artery that frequently accompanies the IIN and IHN

Either in-plane or out-of-plane technique. Use of a short bevel nerve block needle with 5 mL of LA (and steroid) is recommended

Additional information

Previous surgical scarring can alter the sono-anatomy; in such cases, a nerve stimulator can be used to locate the nerves

For the out-of-plane approach, use of hydro-dissection is recommended to identify the needle tip position and avoid localized IM injection

Technique for GFN block

The US probe is placed in the inguinal crease to visualize the femoral artery in short axis; it is then turned by 90° at the level of the internal inguinal ring to visualize the femoral artery in long axis

Moving in a cephalad direction, the artery is seen as diving deep towards the inguinal ligament as it becomes the external iliac artery

At this point, an oval structure can easily be seen super cial to the external iliac artery, opposite the internal inguinal ring (this is the spermatic cord or the round ligament of the uterus)

The nal position of the probe is about two nger-breadths lateral to the pubic tubercle, with the orientation perpendicular to the inguinal line

The GFN cannot be visualized directly

The key structure is the spermatic cord (round ligament of the uterus), which is oval, with one or two arteries within it (the testicular artery and the artery to the vas deferens)

An in-plane or out-of-plane approach with 8 mL of LA and steroids is used

Additional information

Due to the variable location of the genital branch in the GFN, it is recommended to deposit 4 mL of LA inside and another 4 mL outside the spermatic cord

Further reading

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22.4 Shoulder, knee, and hip joint—blocks and denervation procedures

Shoulder joint

Anatomy—innervation

Brachial plexus via the suprascapular nerve (SSN) and axillary nerve

Other contributing nerves: lateral pectoral nerve, subscapular nerves, and musculocutaneous nerve

Majority of innervation is from the suprascapular nerve (posterior shoulder joint capsule, acromioclavicular joint (ACJ), coracoclavicular ligaments, coracoacromial ligament, and subacromial–subdeltoid bursa)

The SSN arises from the upper trunk of the brachial plexus and runs laterally beneath the trapezius and omohyoid muscle and enters in the supraspinous fossa via the suprascapular notch beneath the suprascapular ligament (accompanied by the neuro-vascular bundle)

Suprascapular nerve block

Chronic shoulder pain secondary to rotator cu tear, arthropathy

Adhesive capsulitis

OA, RA

Chronic post-surgical pain after shoulder surgery

Post-operative analgesia following shoulder arthroplasty

Patient refusal

Localized infection

Allergy (LA, steroids)

Patient position: sitting, lateral

Equipment: high-frequency linear US probe (6–13 MHz)

A linear probe is recommended, given that the nerve is quite super cial (<5 cm), with the patient in sitting or lateral position

The US probe is positioned parallel to the scapular spine and then moved anteriorly to visualize the suprascapular fossa and the trapezius and supraspinatus muscles (see Fig. 22.4.1)

The suprascapular artery can be visualized with colour Doppler

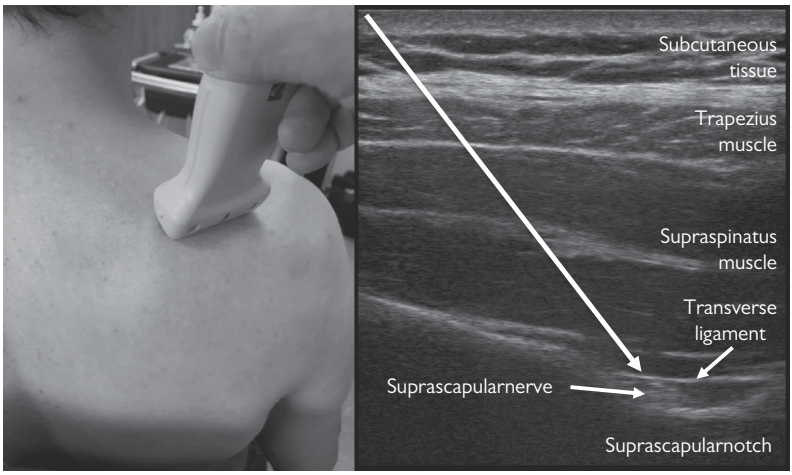
A volume of 5 mL of LA and steroid is injected under real-time guidance using an in-plane or out-of-plane approach

Failure

Infection, bleeding, bruising

Pneumothorax

Nerve injury and injury to blood vessels



Ultrasound image of the suprascapular notch with the suprascapular nerve, white arrow = needle path (Right), Ultrasound probe position (Left)
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The SSN can be targeted either at the suprascapular notch or in the supraclavicular fossa
Targeting the SSN at the notch using a blind or landmark approach increases the risk of pneumothorax, intravascular injections, and nerve injury
This risk can be minimized by placing the needle in the supraclavicular fossa and placing 1–2 ml of LA to block the SSN.

Knee joint

Anatomy—innervation

The knee capsule innervation can be simpli ed into an anterior and a posterior group of nerves called genicular nerves (supero-medial, superolateral, infero-medial, infero-lateral) (see Fig. 22.4.2)

Anterior group of genicular nerve branches:

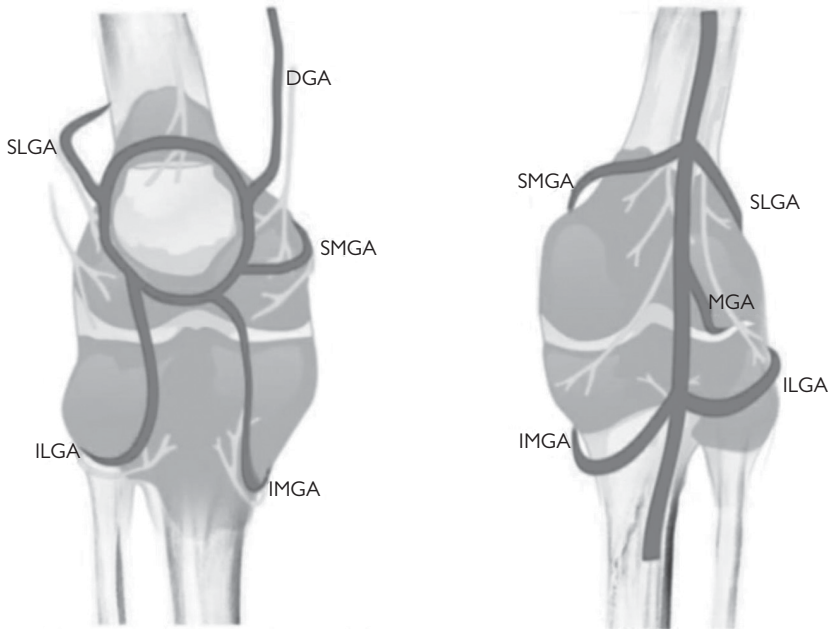
- Femoral nerve (muscular branches to vasti muscles, saphenous nerve)
- Sciatic nerve (common peroneal nerve: recurrent and lateral retinacular branches)

Posterior group of genicular nerve branches:

- Sciatic nerve (tibial branch)
- Obturator nerve (branches of the posterior division)

Knee genicular nerve blocks and radiofrequency treatment

Alternative treatment modality for patients who are not suitable for knee replacements due to comorbidities
Very obese patients
Patients unwilling to undergo surgery
Chronic post-surgical pain after knee replacement

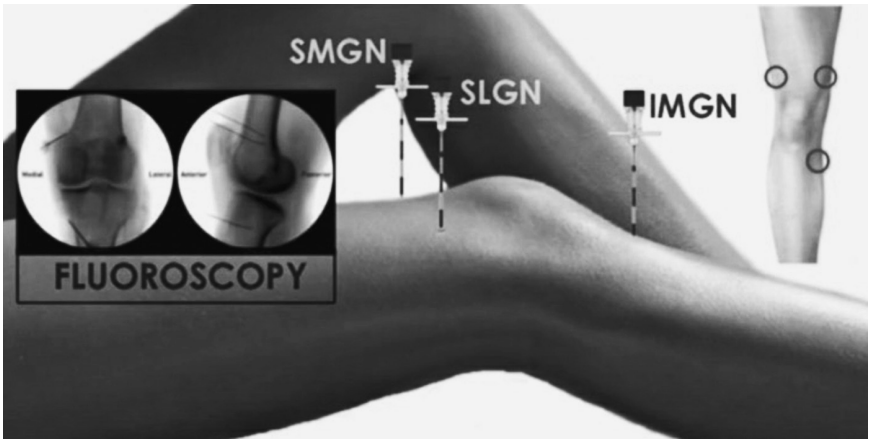


Genicular arteries accompanied by genicular nerves. DGA, descending genicular artery; ILGA, inferior lateral genicular artery; IMGA, inferior medial genicular artery; MGA, middle genicular artery; SLGA, superior lateral genicular artery; SMGA, superior medial genicular artery
Reproduced with permission of Dr Vicente Roqués

Patient refusal
Localized infection
Allergy to LA and steroids
Pacemaker and other implantable devices (relative contraindication for RF)

Patient position: supine
Equipment:
- Linear US probe (6–13 MHZ)
- X-ray and RF generator with 16G or 18G RF needles with 10 mm exposed tips
- A larger needle gauge will provide a bigger lesion size and is recommended

The patient is in supine position, with the knee slightly elevated/ exed
Three genicular branches—superolateral, supero-medial, and infero-medial—are targeted for both diagnostic blocks and RF treatment
For diagnostic blocks, the linear US probe is placed parallel to the femoral shaft and moved caudally to locate the junction between the shaft and the condyle, both medially and laterally, to visualize the supero-medial and superolateral genicular nerves
The US probe is placed parallel to the tibial shaft medially to locate the junction between the tibial shaft and the medial condyle to visualize the infero-medial genicular nerve
The nerves are usually accompanied by arteries



RF treatment of genicular nerves of the knee under uoroscopy guidance. IMGN, inferior medial genicular nerve; SLGN, superior lateral genicular nerve; SMGN, superior medial genicular nerve
Reproduced with permission of Dr Vicente Roqués

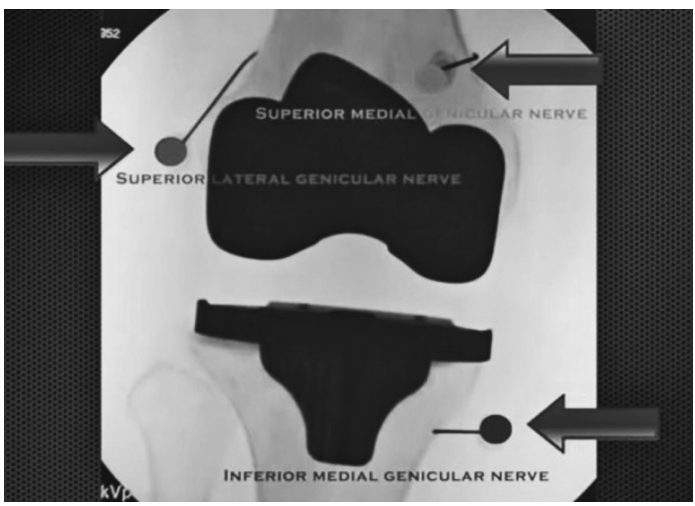
Diagnostic blocks are performed using a 25G, 35 mm needle with an out-of-plane approach using 2–5 mL of LA

The genicular nerves are ablated at the junction of the lateral femoral shaft and the epicondyle, the junction of the medial femoral shaft and the epicondyle, and the junction of the medial tibial shaft and the epicondyle, correspondingly

In addition to the above three nerves, lesioning to the medial (retinacular) genicular branch from the vastus intermedius can be performed at the midline of the femoral shaft just above the patella

AP view and lateral uoroscopy guidance are used to advance the RF needles to meet bony end points

Each nerve is treated with RF lesion of 80°C for 90 seconds, with 25 seconds of ramp time (see Figs. 22.4.3 and 22.4.4)



Supero-medial, superolateral, and infero-medial genicular nerves—radiofrequency needle positioning using uoroscopy guidance
Reproduced with permission of Dr Vicente Roqués

Hip joint

Anatomy—innervation

Innervation to the hip joint capsule is divided into anterior, antero-medial, postero-medial, and postero-lateral areas, which are innervated by the articular branches of the femoral, obturator, sciatic nerve, and superior gluteal nerve, respectively

Hip genicular nerve blocks and radiofrequency treatment

Indications

Alternative treatment modality for patients who are not surgical candidates to undergo hip replacement secondary to comorbidities

Obese patients

Patients unwilling to undergo surgery

Chronic post-surgical pain—post-hip replacement

Contraindications

Patient refusal

Localized infection

Allergy to LA and steroids

Pacemaker and other implantable devices

Equipment

Patient position—supine

X-ray and RF generator with 18G RF needles with 10 mm exposed tips

Technique

To target the sensory branch of the obturator nerve, the tip of the needle is placed under uoroscopy at the site below the inferior junction between the ischium and the pubis. This is a radiological target and is referred to as a teardrop on X-ray. For diagnostic blocks, 1–2 mL of LA is injected after negative aspiration

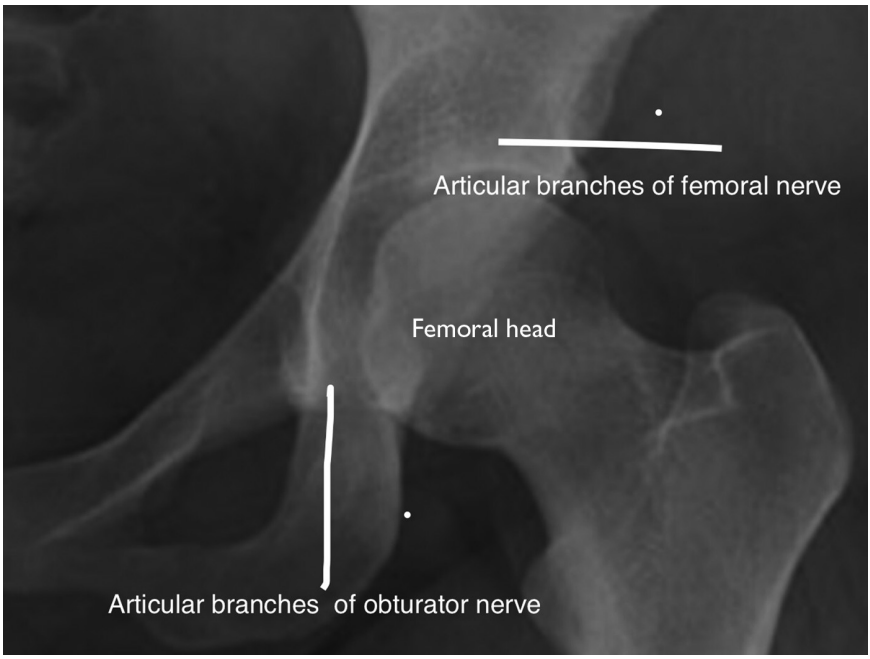
For RF treatment, sensory stimulation is performed to cause paraesthesiae and elicit groin and thigh pain. Motor stimulation is performed to exclude muscle contractions before performing the RF lesion

Femoral nerve articular branches are targeted by inserting the needle using an antero-lateral approach, aiming for the tip of the needle to be placed below the anterior inferior iliac spine near the antero-lateral margin of the hip joint (see Fig 22.4.5). For diagnostic block, 1–2 mL of LA is injected after negative aspiration

Sensory and motor testing is performed to exclude quadriceps muscle contraction

After injection of LA, RF lesion is performed at 80°C for 60–90 seconds

Use of US has been described to block both femoral and obturator articular branches to the hip joint. US can allow the operator to safely avoid critical structures such as blood vessels and increase the safety of the procedure



Targets for needle positioning for radiofrequency lesioning of articular branches (genicular nerves) of the femoral and obturator nerves

Further reading

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2. Franco CD, Buvanendran A, Petersohn JD, et al. Innervation of the anterior capsule of the human knee: implications for radiofrequency ablation. Reg Anesth Pain Med 2015;40(4):363–8
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4. Kawaguchi M, Hashizume K, Iwata T, Furuya H. Percutaneous radiofrequency lesioning of the sensory branches of obturator and femoral nerve for the treatment of hip joint pain. Reg Anesth Pain Med 2001;26:576–81
5. Chaiban G, Paradis T, Atallah J. Use of ultrasound and uoroscopy guidance in percutaneous radiofrequency lesioning of the sensory branches of the femoral and obturator nerves. Pain Pract 2014;14(4):343–5
6. Simpson G, Krol A, Silver D, Nicholls B. Genicular nerves. In: Simpson G, Krol A, Silver D, Nicholls B (eds). Ultrasound-guided Interventions in Chronic Pain Management. 2019; pp. 163–7. UK: European Society of Regional Anaesthesia & Pain Therapy (ESRA)
7. Escolar VR. Ultrasound guided genicular nerve block. 2014. https://www.youtube.com/watch?v=uY93Oekl2j8

22.5 Myofascial trigger point injections

Introduction

Myofascial pain is caused by a complex combination of sensory and motor abnormalities involving the peripheral and central nervous systems. It is characterized by regional pain, muscular tenderness, and the presence of myofascial trigger points (MTrPs)

MTrPs are focally hypersensitive taut bands in muscles. Palpation produces a painful local twitch response or a 'jump sign', characterized by a jump or involuntary re ex-like; reproducible movement of the patient that is disproportionate to the amount of pressure exerted on an MTrP

Palpation of MTrPs normally produces a typical referral pattern

It is not understood why MTrPs occur, but some postulated mechanisms include:

- Focal in ammation leading to sensitization, spontaneous discharge, and mechanical sensitivity of peripheral nerves. There is secondary hyperalgesia and sensitization in the muscles in close proximity to these in amed nerves
- Nociception in deep tissues that can lead to remote localized pain and alteration in central nociceptive processes. This may relegate the MTrPs as sites of secondary allodynia

MTrPs are commonly treated by manipulation with manual pressure or injections

Indications

Symptoms and examination ndings consistent with active MTrPs

Most studies of the evidence/studies are very heterogenous:

- TPIs can be helpful to reduce pain associated with MTrPs
- Majority of the studies have not found strong evidence to support the use of steroids or botulinum toxin
- Some studies have found dry needling as e ective as needling with LA

Contraindications

Systemic or local infection, bleeding disorders or anticoagulation, pregnancy, allergy to LA agents, acute muscle trauma, needle phobia

Mechanism of action

Uncertain, but some of the mechanisms involved in inactivation of the neural feedback mechanisms include:

- Needling-mediated local release of intracellular K^+-disrupting nerve conduction
- Dilution of nerve-sensitizing substances
- Vasodilatation enhancing local removal of metabolites and increasing local energy supply
- Focal necrosis of the trigger point
- Counterirritation or application of a competing noxious stimulus which leads to activation of regions in the brain responsible for anti-nociception
- Placebo e ect

Patient preparation and positioning

Position: prone, supine, or seated position

Solutions: lidocaine or procaine (least myotoxic of all local injectable anaesthetics). Do not use adrenaline

Isotonic saline or dry needling may be used in patients allergic to LAs

Steroids may be considered for ligamentous trigger points

Technique

Digital examination of muscles may exhibit a palpable taut band or cord of tense muscle bres approximately 1–4 mm in diameter. Palpate along this band to locate the point of maximum tenderness. Pressure is held rmly to elicit the referred pain pattern

Once a trigger point has been located and the overlying skin has been cleansed with alcohol, the clinician should isolate the trigger point with a pinch between two ngers, with stabilizing pressure to prevent it from rolling away from the advancing needle. The needle is inserted 1–2 cm away from the trigger point and then advanced into the trigger point at an acute angle of 30° to the skin. Aspirate before injection to avoid intravascular injection

Once the needle is inside the trigger point, a small amount (0.2 mL) of LA is injected. The needle is withdrawn to the level of the SC tissue, then redirected superiorly, inferiorly, laterally, and medially. The needling and injection process is repeated in each direction without withdrawal of the needle, until the local twitch response is extinguished or until the muscle relaxes. Pressure should be applied over injection sites

Complications

Vasovagal syncope, skin infection, pneumothorax (when performed in thorax), needle breakage, haematoma

Special points

The priority is to correct the causative underlying aetiology

It is important to correct other biopsychosocial perpetuating factors such as chronic infections, abnormal postures, nutritional de cits, stress, and sleep disturbances

Stretching and exercise are critical part of the treatment programme in patients that receive a TPI

Further reading

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3. Wong CSM, Wong SHS. A new look at trigger point injections. Anesthesiol Res Pract 2012;2012:492452

22.6 Upper limb blocks

Introduction

This chapter describes blocks for the brachial plexus and peripheral nerves in the arm

Contraindications for these blocks include:

Absolute: patient refusal, local infection, LA allergy

Relative: coagulopathy, systemic infection

Complications that can occur include infection, haematoma, vascular puncture, and nerve injury

The typical volume of LA normally used for brachial plexus blocks is 10-20mls with intermittent aspiration during administration. The speci c LA used depends on the onset and duration of action (maximum dose is calculated per body weight). Other agents that can be used to improve the e cacy of blocks are steroids, adrenaline, bicarbonate, magnesium, clonidine, dexmedetomidine and in palliative procedures neurolytic agents (please refer to Chapter 6, 15 and 29 for further information)

A peripheral nerve stimulator is a useful aid to locate nerves and can improve safety when nerve blocks are performed

Blocks of the brachial plexus

The neck is a highly vascular area, and care must be exercised to avoid intravascular injection, in particular the vertebral, inferior thyroid, suprascapular, and transverse cervical arteries

Visualization is normally best with a high-frequency US linear probe

Most blocks done with a 21G and 5/8/10 cm needle

Anatomy of the brachial plexus

The brachial plexus innervates the shoulders, arms, and hands. It consists of:

Roots: originate from the anterior primary rami of the spinal nerves, C5–T1, that leave through the intervertebral foramina

Trunks: C5–T1 spinal nerves that form the upper (C5–6), middle (C7), and lower (C8–T1) trunks of the brachial plexus

Divisions: each trunk splits into an anterior and posterior division, generally respectively supplying the exor and extensor muscles of the upper limb

Cords: the cords are divided into lateral, median, and posterior, according to their relation to the mid-axillary artery

Terminal branches arise from the cords:

- musculocutaneous nerve – lateral cord
- ulnar nerve – medial cord
- median nerve – lateral & medial cord
- axillary nerve – posterior cord
- radial nerve – posterior cord

Additional branches are dorsal scapular, long thoracic, phrenic, suprascapular, long thoracic, lateral & medial pectoral, medial brachial cutaneous, medial antebrachial cutaneous nerves, and the nerve to the subclavius muscle

Interscalene block

Indications

Analgesia and anaesthesia of the shoulder and upper arm

Speci c contraindications

Contralateral block to avoid bilateral phrenic nerve and recurrent paresis

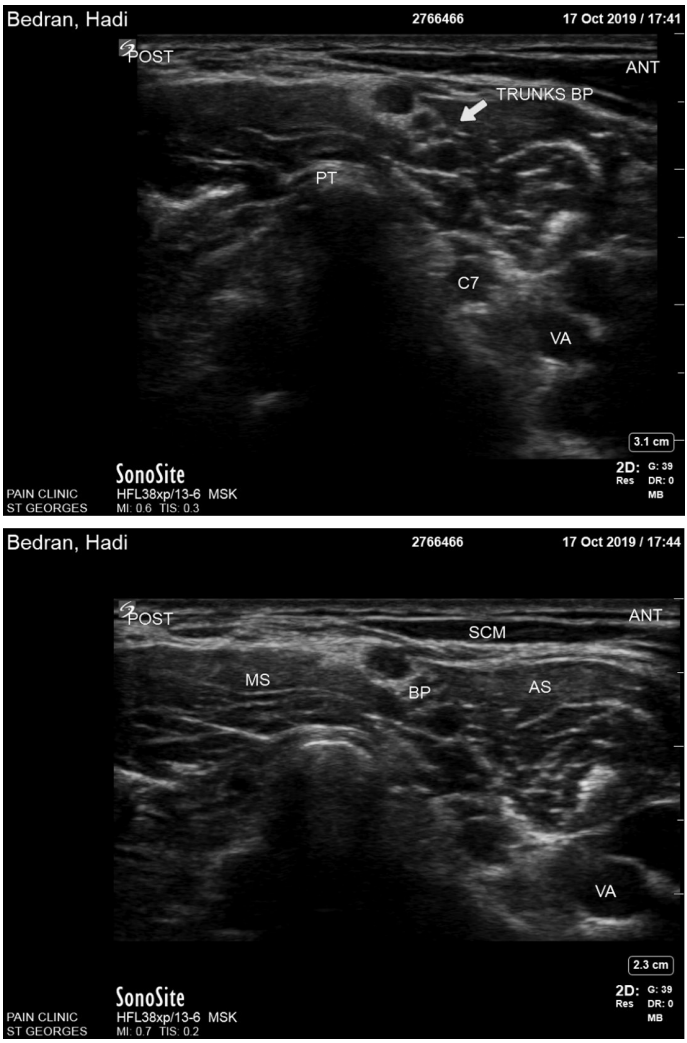
Moderate/severe COPD or limited respiratory reserve

Patient preparation and positioning

Supine, with head slightly rotated to the contralateral side. Ipsilateral arm resting on the patient's thigh

Technique

Block performed at the root or trunk level. The plexus at this level is seen antero-lateral to the carotid artery, between the anterior and middle scalene muscles—typically at 1–3 cm depth (see Fig. 22.6.1)



Interscalene views of the brachial plexus. AS, anterior scalene muscle; BP, brachial plexus; MS, musculocutaneous nerve; PT, posterior tubercle of C7; SCM, sternocleidomastoid muscle; TRUNKS BP, trunks of the brachial plexus; VA, vertebral artery

From the supraclavicular position, the US probe is moved superiorly to an optimal point where the nerve roots can be visualized as round hypoechoic structures between the anterior and medial scalene muscles, but away from the subclavian artery and lung

In-plane or out-of-plane approach. Deposit 15–20 ml LA below C6 and between C5 and C6 under real-time guidance

Disadvantages

May miss C7–T1 (ulnar)—often di cult to visualize as located deeply

80% chance of phrenic nerve palsy—avoid in limited respiratory reserve

Inadvertent epidural/subarachnoid injection, Horner's syndrome (miosis, partial ptosis, apparent anhidrosis, and enophthalmos), unilateral vocal cord palsy, vertebral artery injection, pneumothorax

Advantages

Super cial anatomy

Rapid onset

Supraclavicular block

Indications

Analgesia and anaesthesia of the arm and hand

Speci c contraindications

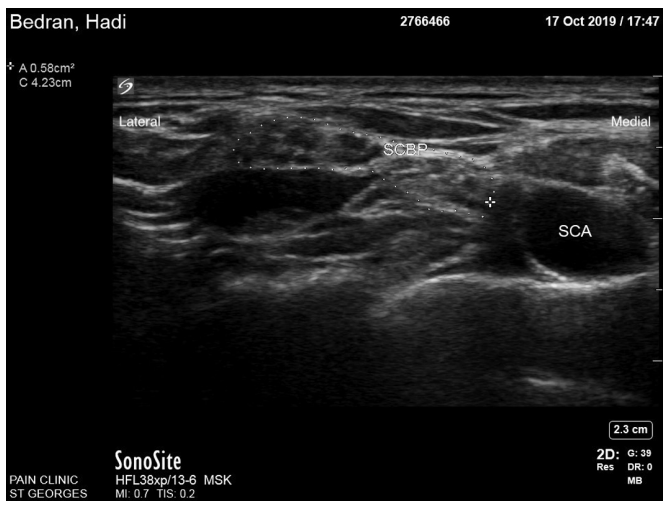
Severe COPD

Patient preparation and positioning

Patient supine, with the head slightly rotated to the contralateral side. Arm abducted with the hand resting on the abdomen

Technique

US probe is placed above and parallel to the clavicle. In the optimal image, the subclavian artery, plexus, and rst rib can be seen. The brachial plexus is normally postero-lateral to the subclavian artery. 15 – 20ml LA can be in ltrated by an in-plane approach at 12, 3, and 5 o'clock to the subclavian artery (see Fig. 22.6.2)



Supraclavicular view of the brachial plexus. SCA, subclavian artery; SCBP, supraclavicular brachial plexus

Disadvantages

Pneumothorax—high risk as it is close to the pleura

Phrenic nerve block (around 50–60% risk)

Subclavian artery puncture—avoid in coagulopathic patients as bleeding is non-compressible

Advantages

Anatomy is usually consistent

Normally easy to visualize—the plexus is clumped together

Infraclavicular block

Indications

Analgesia and anaesthesia of the arm and hand

Speci c contraindications

Clavicle/thorax deformities

Devices in thorax (e.g. cardiac pacemaker)

Coagulopathy (relative) as subclavian vessels are non-compressible

Patient preparation and positioning

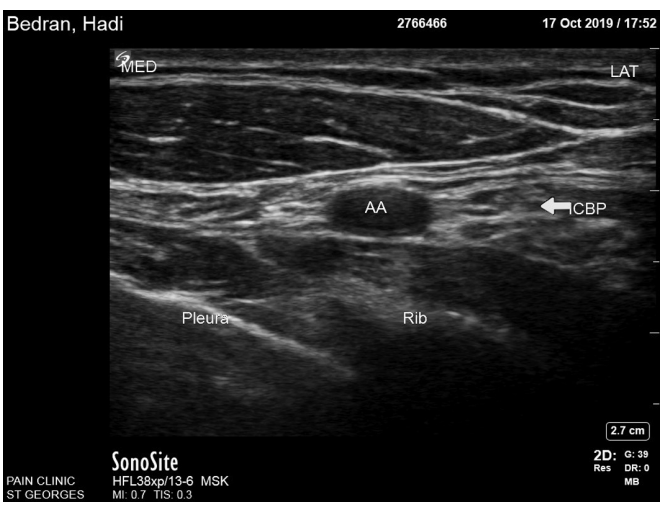
Patient supine, with the head slightly rotated to the contralateral side. Elbow exed and shoulder abducted

Technique

Aim to block the cords, which are arranged around the proximal part of the axillary artery

Place US probe parasagittal, just medial to the coracoid process, to visualize the axillary artery ± vein (see Fig. 22.6.3)

Inject 15 – 20ml LA around the artery via an in-plane approach under real-time guidance



Infraclavicular view of the brachial plexus. AA, axillary artery; ICBP, infraclavicular brachial plexus

Disadvantages

Pneumothorax—retro-clavicular or modi ed classical approach can decrease the risk of puncturing the pleura

Di cult needling technique—can be more di cult in patients with large breasts or who are very muscular. Retro-clavicular and costoclavicular techniques can improve needle visualization

Avoid in coagulopathic patients

Advantages

Anatomy is usually consistent

In patients with limited respiratory reserve an infraclavicular block is better to a supraclavicular/interscalene nerve blocks

Axillary block

Indications

Analgesia and anaesthesia in the forearm and hand

Patient preparation and positioning

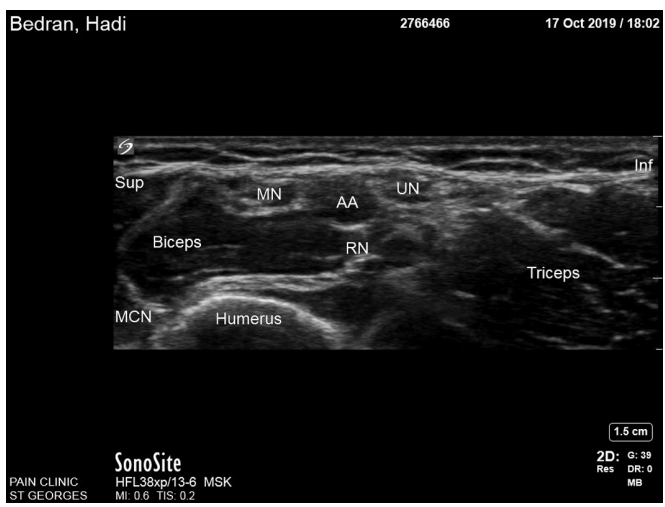
Patient supine, with the head slightly rotated to the contralateral side. Arm abducted with elbow exed

Technique

Aim to block the terminal nerve branches as they pass through the base of the axilla in close proximity to the axillary artery (see Fig. 22.6.4)

The probe across the axilla, aiming to visualize the axillary artery and vein, the coracobrachialis muscle, and the two heads of the biceps

The musculoskeletal nerve is a bright structure between the muscles between the biceps and coracobrachialis muscle and normally above the axillary artery



Axillary view of the brachial plexus. AA, axillary artery; MCN, musculocutaneous nerve; MN, medial nerve; RN, radial nerve; UN, ulnar nerve

The median, ulnar, and radial nerves are seen around the axillary artery (median nerve is above, ulnar nerve is below and radial nerve is below or behind)

Inject 15 – 20ml LA via an in-plane or out-of-plane approach under real-time guidance

Disadvantages

High anatomical variation of the nerves and nerves located in several areas

Sometimes it is di cult to nd the musculocutaneous nerve

Advantages

Compressible if there is any bleeding

Safest approach to the brachial plexus blocks

Additional information

Intercostobrachial nerve block needed in surgery in the axilla/medial aspect of the arm or if a tourniquet is applied on the upper arm. Frequently done with the landmark technique as di cult to see with USS

Peripheral upper limb blocks

Anatomy relevant to blocks

Radial nerve: found in the groove between the lateral border of the biceps tendon and the brachioradialis, 1.5–2 cm proximal to the elbow crease

Median nerve: lies medial to the brachial artery in the antecubital fossa. Enters the hand via the carpal tunnel

Ulnar nerve: enters the forearm beneath the two heads of the exor carpi ulnaris. It joins the ulnar artery along the forearm and runs to the wrist posterior to the artery and deep to the exor carpi ulnaris

Indications

Surgical anaesthesia along the course of the individual nerve

Supplement to brachial plexus block

Radial tunnel syndrome; Cheiralgia paresthetica (Wartenberg's syndrome)

Patient preparation and positioning

The preferred position is supine, with the arm supported on the side

Visualization is best with a high-frequency US linear probe

The forearm should be held in supination for blocking the median nerve. For easy access to the ulnar nerve, the arm can be abducted and the elbow exed. Access to the radial nerve above the elbow is best when the hand is rested over the patient's abdomen

Technique

The typical volume of LA used to block a peripheral nerve is 5-8mls (LA maximum dose is calculated per body weight as outlined in Chapter 6)

Radial nerve:

Place the transducer a few centimetres proximal to the lateral epicondyle of the humerus, transversely across the upper arm

Identify the nerve as a hyperechoic triangular or ovoid structure, which can separate into two branches with distal movement of the transducer

In- or out-of-plane approach is acceptable

Median nerve:

Place the transducer transversely across at the antecubital fossa at the level of the elbow crease

The nerve lies medial to the brachial artery as a distinct hyperechoic structure, either lateral or deep to the pronator teres muscle

Approach in-plane or out-of-plane, preferably injecting on the medial side of the nerve

Ulnar nerve:

Place the transducer transversely across the ulnar border of the proximal mid forearm, scanning distally to identify the ulnar nerve and artery as they come closer to each other

The nerve stays in close proximity to the exor carpi ulnaris

The needle can come from either side of the nerve, aiming to avoid the artery

Further reading

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2. Juels AN, Raghavendra M. Infraclavicular Nerve Block. 2018. https://emedicine.medscape.com/article/2000107-overview
3. Upper Extremity Blocks. NYSORA. https://www.nysora.com/techniques/upper-extremity/

22.7 Lower limb blocks

Introduction

High-frequency linear US probe is suitable for all, except in the very obese

Most blocks are done with 21G and 8/10 cm needle

The typical volume of LA normally used for lower limb blocks is 10-20mls for proximal blocks and 5-10mls for distal individual peripheral lower limb nerves. The speci c agent used depends on the onset and duration of action of the LA (maximum dose is calculated per body weight). Other agents can be used to improve the e cacy of blocks such as steroids, adrenaline, bicarbonate, magnesium, clonidine, dexmedetomidine and neurolytic agents in palliative procedures (please refer to Chapter 6, 15, 29 and 13.8 Clonodine, p. 244 for further information)

A peripheral nerve stimulator is a useful aid to locate the nerve and can improve safety when these nerve blocks are performed

Anatomy

Femoral nerve

The femoral nerve originates from the anterior rami of the L2, L3 and L4 nerve roots

Enters the thigh under the ilio-inguinal ligament lateral to the femoral artery

Divides into anterior and posterior divisions, with the latter giving rise to the saphenous nerve

Supplies all the muscles in the anterior compartment of the thigh

Gives sensory innervation to the antero-medial thigh and medial side of the leg and foot

Contributes articular branches to the knee joint

Obturator nerve

Formed by the anterior primary rami of the L2, L3, and L4 nerves

Runs within the psoas muscle and exits the pelvis via the obturator foramen, dividing into anterior and posterior branches

Both branches give sensory innervation to the hip capsule, a small area in the medial thigh and posterior aspect of the knee joint, respectively

Both branches supply motor fibres to the hip adductors

Saphenous nerve

A terminal sensory branch of the femoral nerve

Accompanies the superficial femoral artery in the subsartorial canal

Exits at the adductor hiatus between the sartorius and gracilis muscles, giving off an infrapatellar branch

Continues to lie subcutaneously to supply the pre-patellar skin and the medial side of the ankle and foot

Sciatic nerve

Formed by the anterior divisions of L4, L5, and S1–S3 nerve roots

Exits the pelvis via the greater sciatic foramen, mostly anterior to the piriformis muscle

Passes between the ischial tuberosity and the greater trochanter, and enters the posterior thigh by passing deep to the long head of the biceps femoris

Usually divides at the apex of the popliteal fossa into the tibial and common perineal nerves

Innervates the muscles of the posterior thigh, entire leg, and foot

The tibial nerve gives sensory branches to the postero- and antero-lateral sides of the leg, and the sole of the foot

The common fibular nerve gives sensory branches to the lateral leg and the dorsum of the foot

Indications

Femoral nerve: analgesia to anterior thigh, hip, and knee surgery

Obturator nerve: analgesia to the hip and medial aspect of the knee

Saphenous nerve: analgesia to the antero-medial aspect of the knee, medial aspect of the lower leg and medial border of the foot

Sciatic nerve block: in combination with a saphenous nerve block, it provides anaesthesia for ankle and foot surgery. Analgesia for hip, knee, and distal surgery on the lower limb

Contraindications

Absolute: patient refusal, local infection, LA allergy

Relative: coagulopathy, systemic infection, pre-existing peripheral neuropathies

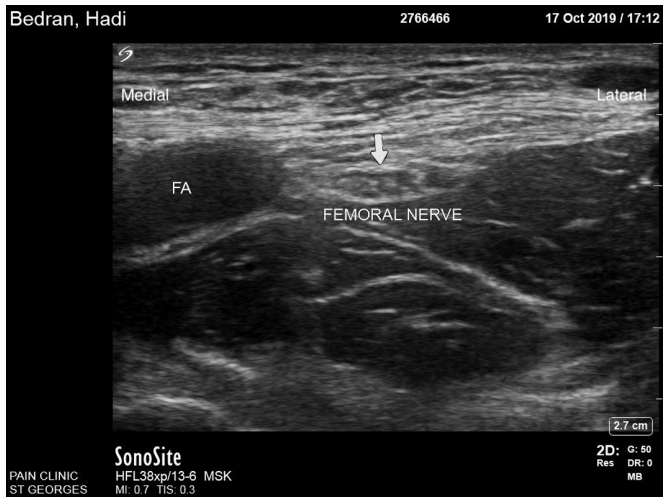
Patient preparation and positioning

Femoral/saphenous nerve: patient supine, with the leg slightly abducted (externally rotated for the obturator nerve)

Sciatic/popliteal nerve: commonly prone or lateral position; supine, with the hip and knee flexed if possible

Technique

Femoral nerve block



Femoral nerve. FA, femoral artery

Place the linear US probe perpendicular to the course of the femoral nerve in the groin, and identify the femoral artery and vein medially just below the inguinal ligament (see Fig. 22.7.1)

Scan laterally to identify the iliacus muscle and fascia iliaca

The nerve is located between the artery and the muscle under the fascia

Inject 15 – 20ml LA via an in-plane or out-of-plane approach under real-time guidance.

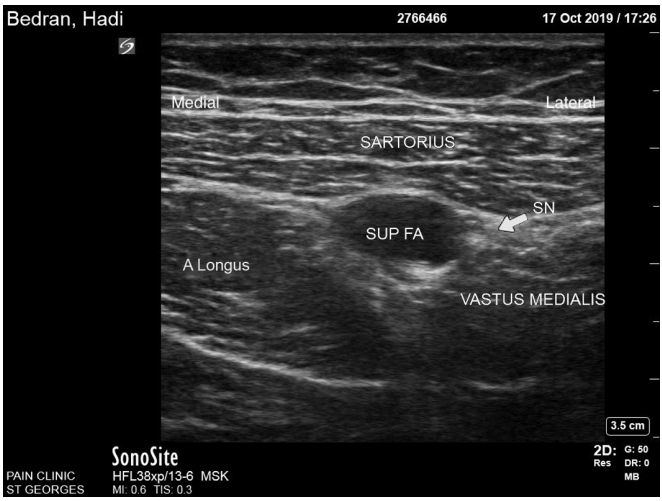
Position the needle lateral to the femoral nerve and below the fascia iliaca

Obturator nerve block

Place the US probe transversely over the inner thigh to identify the femoral artery and vein (see Fig. 22.7.2)



Posterior and anterior obturator nerve branches. A Brevis, adductor brevis; A Longus, adductor longus; A Magnus, adductor magnus; Ant ON, anterior obturator nerve; Post ON, posterior obturator nerve



Saphenous nerve. A Longus, adductor longus; SUP FA, super cial femoral artery; SN, saphenous nerve

Scan medially until the pectineus muscle belly is seen

Continue medially until three muscle layers are visible

From super cial to deep: adductor longus, brevis, and magnus

The anterior and posterior branches of the obturator nerve pass in the planes between the longus and brevis, and the brevis and magnus muscles, respectively

Inject a total of 10 ml LA with an in-plane approach at each branch

Saphenous nerve block

Place the US probe over the mid-thigh (or upper thigh) antero-medially and transversely to view the common femoral artery (see Fig. 22.7.3)

Follow the artery distally until it passes under the sartorius to enter the adductor canal

The femoral vein is seen underneath the muscle and the nerve is lateral to the artery.

Saphenous nerve block can be performed either at the distal femoral triangle where the medial vastus nerve is blocked leading to some muscle weakness or at the mid-thigh level where the vastus medialis nerve may be spared. Blocking the vastus medialis nerve can be bene cial for analgesia to the knee

Inject 10 ml LA via an in-plane or out-of-plane approach under real-time guidance

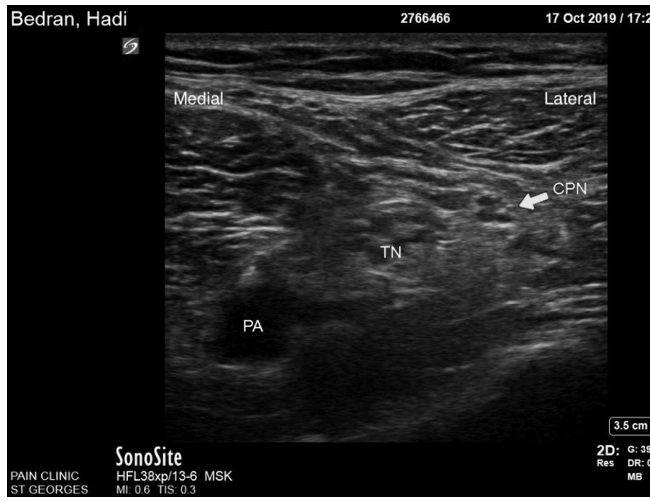
Sciatic (popliteal and mid-thigh) nerve block

Place the transducer transversely over the popliteal fossa, and identify the popliteal artery and vein. The probe may need to be tilted distally and perpendicular to the popliteal sciatic nerve. The tibial nerve is seen super cial to the vein and artery (see Fig. 22.7.4)

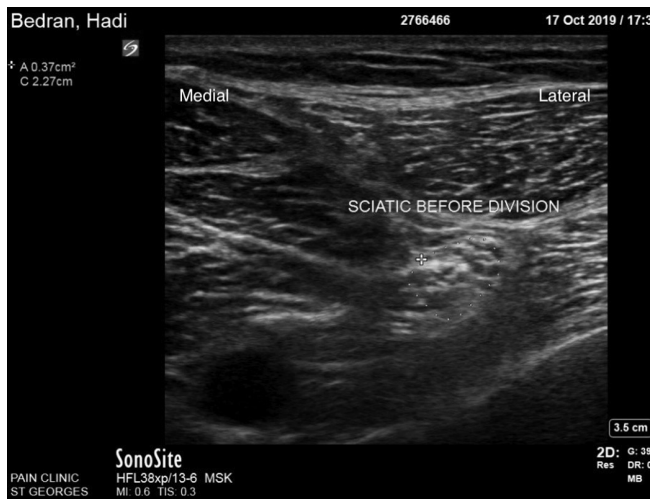
Scanning laterally, the common peroneal nerve can be found underneath the medial border of the biceps femoris. At this level, popliteal block can be performed by inserting the needle in-plane from the lateral side and depositing LA to surround each nerve

To perform a sciatic nerve (mid-thigh) block, scan proximally to the point before the sciatic nerve divides into the femoral and peroneal branches (see Figs. 22.7.5, 22.7.6 and 22.7.7)

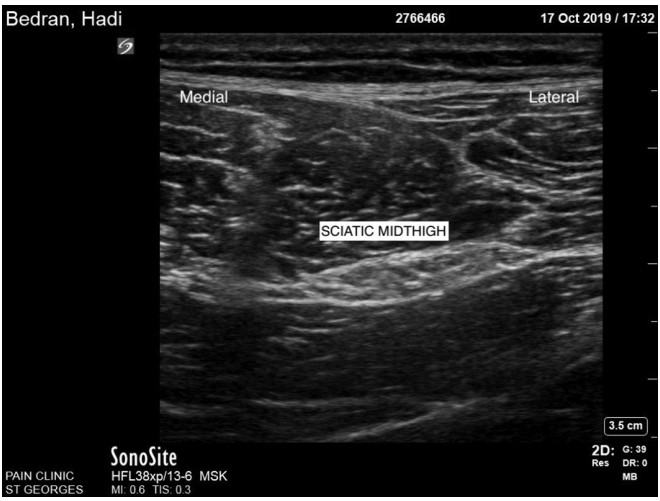
Inject 5 – 20ml LA via an in-plane or out-of-plane approach under real-time guidance. During the injection the perineural sheath needs to be penetrated carefully (without injuring the



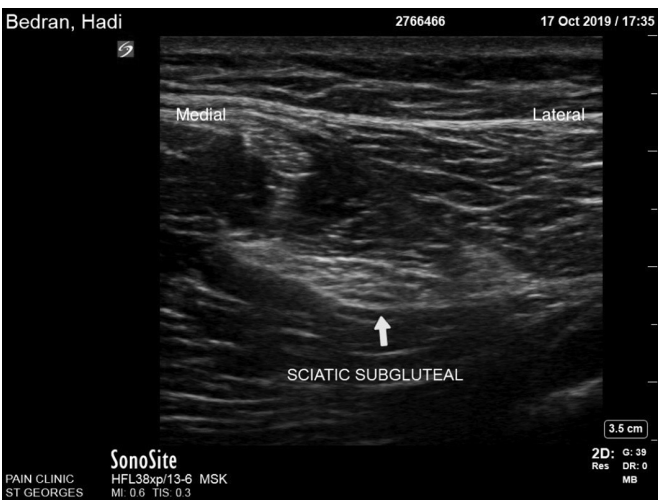
Common peroneal and tibial nerves. CPN, common peroneal nerve; PA, popliteal artery; TN, tibial nerve



Sciatic nerve before division



Sciatic nerve in the mid-thigh region



Sciatic nerve in subgluteal region

nerve). The local anaesthetic is deposited either at the junction or distal to the division of the sciatic nerve into femoral and peroneal divisions. The division of the sciatic nerve is variable but normally occurs above the poplitea or between poplitea and mid-thigh

Special points

Whenever in doubt, the colour ow Doppler mode should be used to identify vascular structures

Further reading

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2. NYSORA (New York School of Regional Anesthesia). https://www.nysora.com

22.8 Suprascapular nerve block

Anatomy

The suprascapular nerve is a mixed nerve

Originates from the superior trunk of the brachial plexus (C5 and C6 nerve roots)

Passes underneath the omohyoid muscle in the posterior triangle of the neck, aiming posteriorly towards the suprascapular notch. It continues deep to the superior transverse scapular ligament through the scapular notch into the supraspinous fossa. After travelling through the supraspinous fossa, the SSN reaches the spinoglenoid notch laterally and exits into the infraspinous fossa

Structures innervated:

- Supraspinatus and infraspinatus muscles
- Sensory innervation to the glenohumeral and acromioclavicular joints, coracohumeral ligament, subacromial bursa, and scapula

At the suprascapular notch, the nerve is next to the suprascapular artery and vein, but the vessels pass above the ligament. From an anatomical perspective, it is best to block the nerve over the supraspinous fossa halfway between the suprascapular notch and the spinoglenoid notch

Indications

Acute shoulder pain

Chronic shoulder pain secondary to bursitis, arthritis, degenerative joint, and rotator cu disease

Contraindications

Absolute: patient refusal, local infection, LA allergy

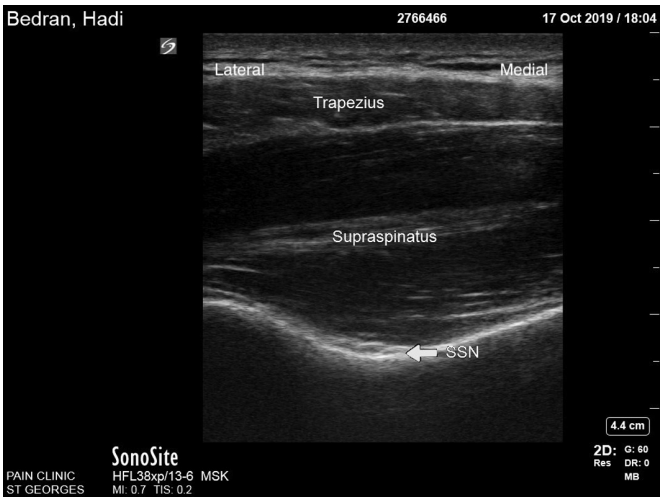
Relative: coagulopathy, systemic infection

Patient preparation and positioning

Position: sitting, ideally placing their hand over to the contralateral shoulder

US probe: 10–12 MHz, linear

Other equipment: 22G, 80–100 mm nerve block/RF needle, peripheral nerve stimulator



Suprascapular nerve block. SSN, suprascapular nerve

Technique

Probe position: place one end of the transducer over the scapular spine and the other end directing towards the coracoid process (see Fig. 22.8.1)

Aim: view of the suprascapular nerve and vessels

US landmarks: supraspinous fossa, suprascapular and spinoglenoid notches, suprascapular muscle, superior transverse scapular ligament

Needle approach: preferably in-plane, aiming from postero-medial to antero-lateral; out-of-plane is also possible. Motor stimulation is recommended

Proposed injectates:

For anaesthesia/acute pain: 5–8 mL of bupivacaine or levobupivacaine 0.5%

In patients with chronic pain, a long-acting steroid, such as 40 mg methylprednisolone, can be added to the above mixture and PRF treatment may be performed at the same time

Complications

Nerve injury, pneumothorax, haematoma, LA toxicity, infection, steroid S/Es if steroids are used

Special points

The optimal needle end point is reached when the needle tip is positioned underneath the fascia of the supraspinatus muscle

Avoid targeting the suprascapular nerve in the suprascapular notch because accidental anterior needle advancement can puncture the pleura anteriorly

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22.9 Vertebroplasty

Introduction

Vertebroplasty and kyphoplasty can be e ective for the management of pain from vertebral fractures from cancer (primary or metastatic), osteoporosis, and trauma. This topic will focus on the role of vertebroplasty in osteoporotic vertebral fractures

Osteoporotic compression fractures (OCFs) are the most common vertebral fractures. Most cause minimal symptoms, but a subset of patients develop severe pain and lose their functional independence. Vertebroplasty has been used to reduce pain and enhance earlier recovery in these patients

The vertebral body comprises trabecular bone surrounded by a thin shell of cortical bone. Osteoporosis reduces the quantity of trabecular bone, causing loss of vertebral body strength. This can result in vertebral fractures secondary to a fall, a lifting or twisting action, or without obvious trigger

Fractures can be divided into three anatomical regions: thoracic (T4–10), thoracolumbar (T11–L2), and lumbar (L3–5). Thoracolumbar fractures comprise 60–80% of severely painful vertebral fractures. These di erent regions are exposed to di erent forces. Thoracic vertebrae are braced against exion forces by the rib cage. The thoracolumbar segment lies below the in exible thoracic spine and is subjected to magni ed compressive exion forces

Osteoporotic vertebral fractures behave di erently to traumatic fractures of healthy bone. Osteoporotic fractures may continue to collapse and change morphology, sometimes developing osteonecrotic clefts and further fracture lines. Such deterioration in fracture morphology occurs in old patients with severe osteoporosis and causes severe fracture pain. Early vertebroplasty in these patients can stop collapse of the bone, stabilize fracture motion, and relieve pain

Evidence

Vertebroplasty evidence remains controversial. A systematic review identi ed 13 randomized trials of vertebroplasty. Five were blinded trials comparing vertebroplasty to placebo, and eight were open comparing vertebroplasty to conservative therapy. A meta-analysis of open randomized trials showed vertebroplasty superior to conservative care.

The VAPOUR trial is the only blinded trial to show superior pain relief from vertebroplasty over placebo. Major differences in patient selection between the VAPOUR trial and other placebo trials include earlier time of vertebroplasty (see Fig. 22.9.1), more severely affected patients, and inclusion of inpatients—excluded in the other blinded trials.

Kyphoplasty is used interchangeably with vertebroplasty, depending upon operator preference. There are no blinded randomized data for kyphoplasty. Three randomized trials comparing kyphoplasty to vertebroplasty have found equivalent clinical outcomes with both techniques. This topic will focus on vertebroplasty.

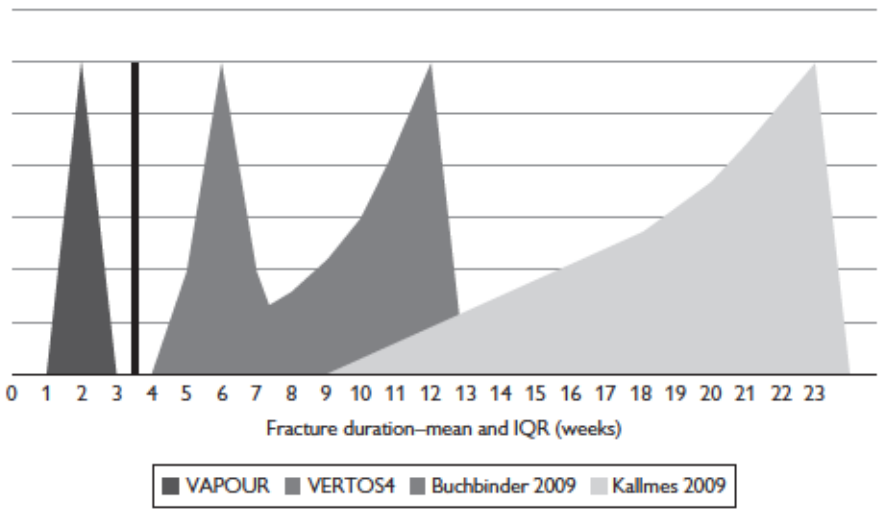


Figure 22.9.1 Fracture duration (mean and interquartile range) in blinded trials of vertebroplasty versus placebo. Note: the mean (triangle apex) and interquartile range (triangle base) of fracture duration is shown for each trial. VAPOUR was the only trial where most patients had fracture duration of <4 weeks. VAPOUR showed vertebroplasty produced superior pain relief to placebo. The other three trials found vertebroplasty and placebo provided equivalent pain relief in older fractures and had different patient groups

Reproduced with permission from Diamond, T., Clark, W., Bird, P. et al. (2020). Early vertebroplasty within 3 weeks of fracture for acute painful vertebral osteoporotic fractures: subgroup analysis of the VAPOUR trial and review of the literature. *Eur Spine J*, 29: 1606–1613. https://doi.org/10.1007/s00586-020-06362-2

Anatomy of vertebral body

- OCFs occur from T4 to L5
- Vertebral bodies increase in size from T4 to L5
- Average volume of T6 is 12 cc^3 and L5 is 45 cc^3
- Vertebral bodies comprise a shell of cortical bone surrounding trabecular bone
- The trabecular bone is the component that fractures

Natural history of OCFs

- Most cause mild symptoms and have a favourable natural history
- A subset of patients with increased age (mean 80 years old), severe osteoporosis, and comorbidities experience uncontrolled severe pain and progressive collapse of the fracture—sometimes with retropulsion into the spinal canal
- 'Dynamic mobility' describes a change in fractured vertebral body height in supine and upright postures. This causes severe pain when attempting to get out of bed
- Patients with severe pain, osteoporosis, and early fractures, including hospitalized patients, do poorly with conservative care

Symptoms

- Pain is typically felt four levels below the anatomical site of fracture. For example, L1 fracture typically causes pain in the buttocks
- Pain has a midline component

Pain is normally described as worse when getting out of bed

Loss of functional independence may necessitate hospitalization

Mechanics of vertebroplasty

Vertebroplasty can stabilize soft, non-healed fractures which have not sclerosed. The best predictor of the degree of fracture healing is fracture duration. The next best indicator is MRI. During vertebroplasty, the injected polymethylmethacrylate (PMMA) cement distributes from top to bottom, side to side, and the anterior 70% of the vertebral body. The distribution of the cement provides stability against exion and compression forces on the vertebral body

Patient selection

Severe pain not responding to medical therapy

Intolerance of opioid medications

Pain duration <4 weeks at time of vertebroplasty

Established osteoporosis—quantitative CT lumbar T-score < 2.5

MRI con rms acute fracture

Thoracolumbar segment responds best to vertebroplasty (T11, T12, L1, L2)

Vertebroplasty procedure

High-viscosity PMMA

Patient prone

Conscious sedation—IV midazolam, fentanyl

Oxygen mask/pulse oximetry monitor

High-quality interventional uoroscope

Tilt cranio-caudad until the pedicles project midway between the superior and inferior endplates

Tilt side-to-side until the spinous process is midway between the pedicles

From this 'neutral' point, angle an additional 20° right posterior oblique

LA into the posterior pedicle

Pass an 11G or 13G needle through the pedicle in this projection

Check the frontal and lateral projections intermittently—ensure the needle does not pass medial to the pedicle (frontal plane) before reaching the posterior cortex of the vertebral body (lateral plane)

Advance the needle to the anterior third of the vertebral body—so the tip is in the midline

Repeat needle insertion on the contralateral pedicle

Inject a small aliquot of PMMA out of the tip of each needle and then wait 60 seconds. This helps prevent venous extravasation

Adjust the technique, depending on fracture morphology

The fracture cleft will be the space of least resistance. Once PMMA nds its way to this cavity, it will preferentially ll it rather than the trabecular bone. To stabilize the whole bone, place at least one needle into normal trabecular bone (away from the cleft). Fill trabecular bone rst—PMMA will nd a way to the cavity and then try to ll both components su ciently to bond them

If necessary, needles can be progressively withdrawn into the posterior half of the vertebral body to allow lling of at least the anterior two-thirds of the vertebral body

If PMMA begins to extravasate, cease the injection; check the position of extravasation in both frontal and lateral projections and wait 30 seconds. Gently recommence injection, initially from

the contralateral needle, and watch for extravasation closely. If extravasation continues, cease the injection.

Recovery

Wait for 5 minutes after completion of the injection before transferring the patient

Allow 1–2 hours for recovery before mobilizing as needed

Medical therapy

Medical osteoporosis management should be optimized

Best indicator of the degree of osteoporosis is the quantitative CT score of the lumbar spine

Patient education on how to avoid bending and lifting is important

Further reading

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22.10 Prolotherapy

History

First description of joint stabilization by Hippocrates who recorded the use of cautery in the axillary esh to stabilize recurrent shoulder dislocation

Injection of broproliferants to strengthen connective tissue has been in use since 1832 (sclerosants for inguinal hernias by Jaynes and Velpeau)

Mayer (1900) reported on the use of zinc sulphate/phenol for hernia repair

In 1935, Mayer showed broproliferation in mammalian connective tissue

The rst modern record was by G Hackett in 1955 who described joint stabilization in rats

In 1956, Hackett published his monograph on 1600 cases of back and neck pain caused by incompetent ligamentous tissue (whiplash and industrial accidents in Ohio), claiming a cure rate of 82% in 1600 patients with low back pain

Progress was delayed by reports of three cases of paralysis and two deaths after inadvertent injection of psyllium seed and zinc sulphate into the subarachnoid space by other practitioners

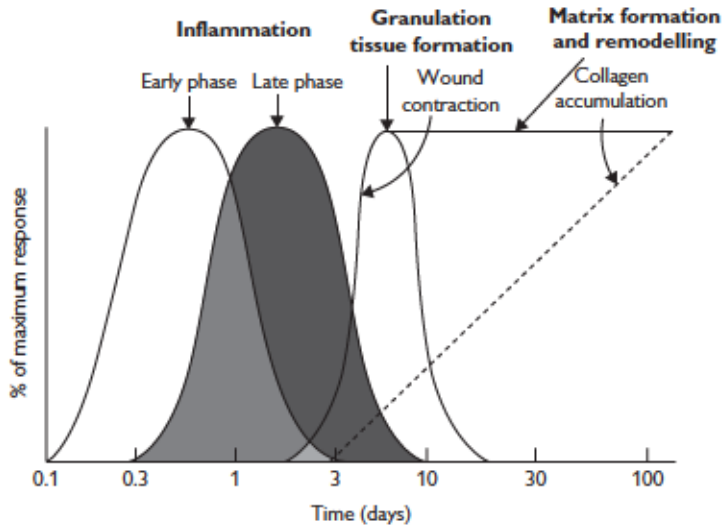


Figure 22.10.1 Inflammatory repair response

- In 1960, MJ Ongley developed a safer solution—vein sclerosant 2% phenol, 25% glucose, 25% glycerol (no serious complications since)
- Since then, several RCTs have been undertaken on heterogenous samples of low back pain patients, with mixed results
- However, use of prolotherapy in sports and exercise medicine has grown and several studies have shown benefit in peripheral joints and conditions

Mechanisms

(See Fig. 22.10.1.)

- Fibroproliferative injection of hypertonic glucose (now more often without phenol) has been shown in animal studies to induce fibroplasia and collagen stimulation and formation, resulting in thicker stronger tissue
- Sample human biopsy tissue from the sacroiliac ligaments pre- and post-injection demonstrated increased fibre density and fibroblast population

Current evidence

- There is level A–C evidence for prolotherapy in various peripheral structures
- Cusi demonstrated benefit for chronic SIJ dysfunction and showed SPECT scan hybrid sequences could accurately identify patients with chronic ligamentous changes in the posterior SIJ ligaments
- Problems with studies on low back pain are numerous: no subgroups were defined; volume, number, and type of proliferant solution varied; confounding existed; some samples were extremely chronic; and no image guidance was used. As a result, it is not recommended by guidelines in the UK at the moment.



Injection sites for lumbar/sacroiliac instability syndrome

This author's experience of over 25 years in 'clinical instability' disorders, sacroiliac dysfunction, whiplash symptoms, and discogenic pain, as well as chronic ankle ligament laxity and ACJ disruption, is rewarding

Clinical audits over the last decade have found that between 70% and 90% show a 'good to excellent' response on a global perceived bene t scale

Technique

Mix P2G solution (2% phenol, 25% glucose, and 25% glycerol), with equal volume of 1% lidocaine

Inject 0.5 mL at either end of enthesis or ligament. Inject as many accessible ligamentous attachments as possible

Repeat at least three times or more at intervals of 1–6 weeks apart to accumulate the e ect

Restoration and remodelling follow the normal pathway of connective tissue healing

Use in low back pain

(See Fig. 22.10.2.)

The bene t may not be felt for 1–3 months after the course since full restoration of collagen matrix takes 120 days or more, but can last longer than other current pain intervention for the low back, except spinal or SIJ fusion. Average relief can range for up to 5–10 years

Further reading

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SECTION 5

CLINICAL

CHAPTER 23

Musculoskeletal Pain Conditions

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23.1 Osteoarthritis

De nition

A disease of synovial joints characterized by cartilage loss with an accompanying periarticular bone response. All joints can be a ected, but more common in the hips, knees, and lumbar spine, compared to mobile joints of the hands or neck

Incidence

8.75 million people in the UK have sought treatment for OA. Women are more likely to seek help than men. The incidence increases with age, from 33% of people over the age of 45 to 49% of women and 42% of men at ages over 75. The most common joints are the knee (18% of the population) and hip (11%)

More prevalent in European countries than in America

OA of the knee is more common than hip OA in African-Americans, South-Asian Indians, and Chinese

Pathophysiology

Progressive loss of synovial cartilage with failure of replacement with new cartilage. Instead there is increased subchondral plate thickness, development of subchondral cysts, and new bone formation. Further structural bone changes alter the articular surface, creating abnormal biomechanical stresses, further aggravating the problems

Aetiology/risk factors

Increasing age, female sex, family history, injury, infection, occupation, obesity, congenital deformities

Trauma to the local joint speeds up the degenerative process

Athletes su er more from OA due to severe and recurrent stress/injury to the joint

Diagnosis

History and examination—pain which worsens on activity, sti ness of the joint in the morning or after inactivity, may be associated with redness and swelling

Investigations—blood tests to rule out infection and in ammatory arthropathies

No radiological imaging is needed if the patient ful ls the following criteria: age over 45, pain on movement or use, sti ness after use, and no evidence of infection

Early radiological changes are of uneven joint space narrowing, progressing to osteophyte and cyst formation, subchondral sclerosis, and subluxations in more severe disease

Di erential diagnosis

Infection, in ammation, trauma, damage to nearby structure (ligaments, etc.), chronic widespread pain, malignancy

Treatment

Goals are pain management and optimizing function

Education and physical therapy

Multidisciplinary approach providing patient with information regarding activity, exercise (local muscle strengthening and general aerobic tness), manipulation and stretching therapy, weight loss, and educational material to enhance understanding and self-management

Non-pharmacological

TENS, heat, and cold topical applications could be considered. Adjuncts such as braces, joint supports, insoles, and assisting devices, such as walking aids, can be o ered. Acupuncture for OA is not recommended.

Pharmacological

First-line management—paracetamol and topical NSAIDs and topical capsaicin can be considered as adjuncts

Oral NSAIDs or COX-2 inhibitors (with a proton pump inhibitor) are also recommended as second-line treatment

NICE 2008 guidance recommends consideration of opiates as second line, and more recent guidance suggests caution and should be reserved for acute are-ups only

Oral/parenteral steroids should not be used as treatment for OA, but injection into the joint can be helpful for symptomatic relief

Glucosamine and chondroitin sulphate supplements have been trialled, with con icting evidence. It slows down degeneration in OA of the knee by stimulating the synthesis of proteoglycans. Not recommended by NICE

Surgery

Joint replacement should be considered when pain limits QoL, but after basic conservative therapies have been tried

Outcome is better in knee OA than with conservative treatment

Outcome of surgery is multifactorial; predictors include preoperative pain and function (the worse the level, the worse the outcome), the presence of anxiety or depression, and social deprivation (poorer patients did less well)

Arthroscopic surgery has been shown to be ine ective for knee OA

Pain interventions

Intra-articular steroid can also be used as an adjunct, although evidence of sustained bene ts for some joints remains poor. Frequent steroid injections can worsen cartilage damage

Hyaluronic acid (not recommended by NICE) and platelet-rich plasma (PRP) have also been used for joint injections

For refractory pains, other interventions, such as suprascapular nerve blocks for shoulder pain or genicular nerve blocks for knee pain, have been used, although the evidence base is still evolving

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23.2 Cervicogenic headache

Introduction

Syndrome characterized by chronic hemicranial pain that is referred to the head from either bony or soft tissue structures in the neck (see Table 23.2.1)

Cervicogenic headache is often misdiagnosed and mistreated. Early diagnosis and multidisciplinary management can reduce disability

Pathophysiology

Pain arising from structures in the neck (facet joints, intervertebral discs, muscles and ligaments) innervated by the trigeminocervical nucleus

The trigeminocervical nucleus is made from:

- Functional convergence of upper cervical (C1–C3) and trigeminal sensory pathways
- The spinal nucleus of the trigeminal nerve extending caudally to the outer lamina of the DH of C1–C3 or C4 spinal segments
- Functional sensorimotor convergence of CN XI (spinal accessory nerve) and the upper cervical nerve roots

Common sources of pain include:

- Atlanto-axial joints
- C2–C3 zygo-apophyseal joints and intervertebral disc
- Upper cervical spinal nerves and roots

Table 23.2.1 Diagnosis of cervicogenic headache

Features	Pain referred from a source in the neck and perceived in one or more regions of the head and/or face
Evidence	Clinical, laboratory, and imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck Demonstration of clinical signs that imply the source of the pain is in the neck (must have demonstrable validity and reliability)
Response to treatment	Abolition of headache following a diagnostic block of a cervical structure or its nerve supply using placebo or other adequate controls. Abolition of headache means complete relief of headache, indicated by a score of 0 on a visual analogue scale Pain resolves within 3 months after successful treatment of the causative disorder or lesion

Source: Data from *The International Classi cation of Headache Disorders*, Third Edition. London, United Kingdom: International Headache Society.

Di erential diagnosis

Posterior cranial fossa lesions, vertebral artery aneurysm, sinus thrombosis, tumours/fractures/infections of upper cervical spine

Cervical spondylosis, osteochondritis, RA, myofascial neck pain

Migraine (without aura), tension headache, cluster headache, hemicrania continua, chronic paroxysmal hemicrania

Functional headache disorder, somatoform disorder

Treatment

Multidisciplinary and multimodal treatments:

- Education on pain management
- Physiotherapy, OT, psychological treatments as per standard chronic pain medicine management
- TENS—limited e cacy
- Medications (anticonvulsants, antidepressants, gabapentinoids)—limited e cacy
- Pain medicine interventions (see Chapter 15):
  - GON block ± PRF
  - LON block ± PRF
  - TON block ± PRF
  - C2–4 facet injections, MBB ± thermal RF (bear in mind C3 supplies C2–3 facet joints)
  - Cervical epidural, DRG block
  - ONS

Surgery

Performed in highly selected patients:

- Transection of GON—beware of S/Es as *anaesthesia dolo*rosa
- Microvascular decompression of the C1–3 DRG
- Neurectomy
- Dorsal rhizotomy

Further reading

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23.3 Neck pain

Introduction

About half of patients with neck pain have predominantly neuropathic or mixed neuropathic–nociceptive symptoms. Patients with neuropathic pain have higher levels of functional impairment and psychological issues

Incidence

Annual prevalence 37.2%; lifetime prevalence 48.5%

Peak prevalence = middle age

Clinical course

Most acute episodes resolve spontaneously within 2 months. Half have low-grade symptoms or recurrence >1 year later

Prediction of pain persistence: genetic and psychosocial factors, female, older age, higher baseline intensity, multiple sites

Prognosis: not impacted on by early treatment or image-proven degeneration

General risk factors

Trauma:

- Sporting injuries: highest incidence in race car driving, wrestling, and ice hockey
- Work-related: o ce workers, manual labour, health care, occupational drivers.
- Exacerbated by low job satisfaction and poor perception of occupational support

Poor general health

Classi cation

Acute versus chronic

Associated with occipital headaches or not

Neuropathic versus non-neuropathic:

43% non-neuropathic pain (nociceptive), 7% neuropathic pain (de ned as neck and arm pain, not arm pain alone), 50% mixed pain

History

Suspected neuropathic pain:

Intervertebral disc herniation:

Nerve root compression due to acute disc herniation will initially produce neck pain, then arm pain

Typical dermatomal pattern, considerable overlap in >50% owing to multiple nerve root involvement

Foraminal stenosis:

Root compression here tends to have an insidious onset

Exacerbated by activities that subarachnoid pressure, e.g. coughing

Cervical spinal stenosis:

Neck pain, sti ness, upper limb radicular pain

Upper motor neuron (UMN) impairment secondary to consequential cervical myelopathy

If associated with fasciculations and bulbar signs, suspect amyotrophic lateral stenosis

Mechanical non-radicular neck pain:

Insidious onset

Facet arthrosis:

Referral patterns helpful in diagnosis:

Atlanto-occipital, atlanto-axial → occipital, posterior auricular

C2/3, C3/4 → occipital, suboccipital

C4/5, C5/6 → shoulder

C6/7, C7/T1 → mid back, scapula

Does not extend distal to shoulder; no associated neurological de cit

Discogenic:

Axial neck pain associated with headaches, uni-/bilateral shoulder pain, non-radicular arm pain, ocular and vestibular dysfunction, anterior chest wall pain

Provoked by coughing, lifting, and applying pressure over cervical spinous processes. Relieved by lying supine

Examination

Signs of nerve root compression may be obscured by MTrPs (coexisting in >50%)

Inspection:

Atrophy of upper extremity muscles; indicator of chronicity and nerve root dysfunction

Numbness in hands is not speci c; can be indicative of carpal and cubital tunnel syndrome

Manoeuvres:

Shoulder pain during rotation and abduction of the upper limb suggests a primary shoulder problem

Speci c tests more accurate for acute > chronic radiculopathy and disc herniation > stenosis

Red ags

Age <20 years: rule out congenital abnormalities, infections

Age >50 years: history of cancer**,** vascular disease

Fever, neck sti ness, nausea or vomiting, unexplained weight loss, torticollis, limited neck mobility, erythema or exudate, severe neck tenderness

Neurological signs such as Ho mann's and Babinski's sign, hyperre exia, altered muscle tone, incontinence, altered cognitive status, ataxia, visual loss, severe headache, and photophobia

Raised in ammatory markers

Investigations

Diagnostic imaging recommended for neuropathic neck pain

MRI superior, needs to be interpreted in clinical context

Consider brachial plexopathy in patients with non-diagnostic imaging, in association with upper extremity pain, weakness, and sensory loss

EMG and NCS (note: sensitivity is 50–71%):

- To con rm existence of nerve root dysfunction
- To exclude other peripheral nerve disorders
- To identify which nerve root(s) are involved and the type of dysfunction (demyelination, axonal loss, conduction block)

Provocation discography (limited evidence)

Mechanical (non-neuropathic) neck pain causes

Non-speci c neck pain

Transformation of neck exors from type I → type II bres, e ects on endurance and strength → fatigue and discomfort

Deep neck muscles (longus colli, longus capitus, rectus capitus) are found to be dysfunctional

Myofascial pain

Involves discrete or di use areas of sensitivity within 1 muscle

May be secondary to biochemical imbalance, trauma, emotional stress, and endocrine and hormonal abnormalities

Palpable trigger points—taut muscle bands that refer pain in a de ned pattern. Primary trigger points often elicit remote trigger points → sti ness, spasms, muscle bre shortening, and reduced strength

Acute or insidious onset, axial neck pain, possibly referred to the shoulders and mid back

Paraspinal tenderness and guarding, reduced range of movement (ROM), no neurological de cit

Treatment:

- Correct underlying structural and postural imbalance
- Physical therapy, including massage, laser, and US, can be e ective
- Pharmacotherapy
- Psychotherapy, including CBT and biofeedback
- TPIs can be considered as adjunct—weak evidence

Cervical facet joint pain

Risk factors: Road tra c accident, trauma, whiplash

Prevalence: 40–55%

Insidious onset of axial neck pain, referred to the occiput, shoulder, mid back

Reduced ROM, paraspinal tenderness, no neurological de cit

Plain lms: weak association with arthrosis

Cervical discogenic pain

Risk factors: smoking, older age, trauma, repetitive neck motions

Prevalence: >70% of patients without pain have signi cant disc degeneration by their mid-forties, and >85% by 60 years

Disc degeneration increases the likelihood of herniation

Insidious onset

Axial neck and shoulder pain, arm pain (non-radicular), vestibular ndings

Reduced ROM (extension > exion, lateral exion > rotation), midline tenderness

Plain films: reduced disc height. MRI: annular tears or fissures

Treatment:

- Surgery is often the mainstay; options include cervical disc arthroplasty (CDA) and fusion
- Evidence for epidural injections, intradiscal injections, and thermal ablation is weak and inconsistent

Neuropathic neck pain causes

Cervical disc herniation

Annual incidence: 1–3.5/1000; most common in 60-year olds; male = female; C7 (45–60%), C6 (20–25%), C5 and C8 (10%)

Acute onset. Not all symptoms are related to nerve root compression. Cytokines and other inflammatory mediators play a crucial role in radicular pain

Approximately 50% of cervical disc herniations will decrease within 6 months; 75% will decrease by >50% within 2 years

Neck pain, myotomal pattern weakness, dermatomal sensory changes

Spurling's test: 40–50% sensitive, 85–95% specific

Shoulder abduction: 40–50% sensitive, 80–90% specific

Neck distraction: 40–50% sensitive, 90% specific

Upper limb tension: 70–90% sensitive, 15–30% specific

Valsalva: 22% sensitive, 94% specific

MRI for nerve root compression: false positive 45%, false negative 26%. CT/CT myelogram: to differentiate between osteophytes and soft tissue changes. EMG: 50–71% sensitive, 85% specific

Treatment:

- Evidence in favour of transforaminal ESIs
- Anti-neuropathic medication

Cervical spinal stenosis

Central, involvement of lateral recesses and/or foramina

Risk factors: advancing age, congenitally small spinal canal, genetics, possibly occupation (e.g. porters, aviation, rugby players)

Incidence: 1:100 000 (for central stenosis where spinal canal diameter <10 mm). Significant >50 years, does not regress with time

Most common cause in adults = degenerative spondylosis

Insidious onset of neck pain and stiffness, radicular pain

Non-specific, but include reduced ROM and paraspinal tenderness

Often → multi-level neuropathic symptoms

MRI: soft tissue evaluation. CT: osseous diameter of spinal canal. EMG: for radiculopathy

Cervical myelopathy

Spinal stenosis associated with spinal cord compression resulting from disease (e.g. myelitis) or injury (e.g. trauma, syrinx), or in older patients = spondylosis

Proposed pathogenesis: chronic neurogenic compression, spinal cord and nerve root ischaemia secondary to venous congestion

Risks factors: age >50 years, male, spinal cord trauma, syrinx

Insidious onset of neck pain, upper limb sensory and motor deficit, gait and balance deficit, incontinence, reduced dexterity

Natural course—highly variable. Periods of quiescence and stepwise progression

Lhermitte's sign: <20% sensitive, >90% speci c

Ho mann's sign: 50–80% sensitive, 78% speci c

Babinski's re ex: 10–70% sensitive, >90% speci c

Hyperre exia: >65% sensitive

Clonus: <50% sensitive

MRI: for intramedullary hyperintensity. EMG: for spinal cord conduction de cits and anterior horn cell dysfunction

Treatment:

- Randomized trials found superior analgesia and mobility with steroid/LA epidurals, compared with the same solution given IM
- Sometimes an indication for surgery; mixed outcomes for surgical and conservative management
- Spondylotic myelopathy—substantial proportion of patients deteriorate, necessitating surgery. Consensus statement on conservative management: 20–60% will deteriorate at 3- to 6-year follow-up

Management

Pharmacological:

- NSAIDs: moderate evidence that topical NSAIDs are e ective for acute and chronic neck pain. Weak evidence supports muscle relaxants for subacute neck pain associated with muscle spasm. Neither drug is superior to non-pharmacological alternative therapies

Interventional (see 16.5 Cervical facet joint/medial branch blocks and radiofrequency denervation, p. 309; 20.5 Epidural injections (cervical, thoracic, lumbar), p. 377):

- Blocks are usually 'diagnostic'

Complementary and alternative therapies:

- Strongest evidence is for exercise
- Weaker evidence supports massage, acupuncture, yoga, and spinal manipulation
- RCT showed spinal manipulation and exercise groups to have statistically signi cant improved outcomes with pharmacological treatment

Surgery:

- More e ective than conservative management in short term, but not long term
- Cervical radiculopathy: anterior cervical discectomy and fusion (ACDF) + physiotherapy versus physiotherapy alone showed surgical group to have less pain and disability at 5 and 8 years, but no di erence in arm pain
- Cervical spondylotic myelopathy: one study showed no di erence in outcomes at 2 and 10 years between conservative management and surgery. Surgery associated with complication rates of 11–38%
- Since only modest short-term bene ts with surgery, conservative management and surveillance for neurological progression are reasonable
- Cervical degenerative disc disease: ACDF and CDA. Scant research comparing with non-surgical outcomes

Conclusions

Topical NSAIDs can be bene cial in non-speci c neck pain

Can use muscle relaxants for acute non-radicular pain

Weak evidence to support ESI in cervical radiculopathy

Weak evidence to support RF ablation in patients with a positive response to diagnostic block

Further reading

1. Cohen SP, Hooten WM. Advances in the diagnosis and management of neck pain. BMJ 2017;358:j3221
2. Tsui SL, Chen PP, Jacobus NG KF. Neck pain. In: Chin PH (ed). Pain Medicine: A Multidisciplinary Approach. 2010; pp. 199–205. Tin Wan: Hong Kong University Press

23.4 Whiplash injury

De nition

Whiplash-associated disorders (WADs) are de ned by the Quebec Task Force as: '*Whiplash is an acceleration–deceleration mechanism of energy transfer to the neck. It may result from rear-end or side-impact motor vehicle collisions, but can also occur during diving or other mishaps. The impact may result in bony or soft-tissue injuries (whiplash-injury), which in turn may lead to a variety of clinical manifestations called Whiplash-Associated Disorders*' (See Table 23.4.1 for classi cation of WADs)

Common injury associated with vehicular collisions

Table 23.4.1 Classi cation of whiplash-associated disorders

Grade	Symptom	Radiography	Treatment
0	Asymptomatic	Not required	Not required
I	Neck pain/sti ness/ tenderness; no physical signs	Not required	Simple analgesics
II	Neck pain/sti ness/ tenderness on palpation, with decreased range of movement	X-ray of cervical spine usually NOT required unless: Suspected bony injury Impaired consciousness High speed impact	Non-opioid analgesics NSAIDs
III	Neck pain/sti ness/ tenderness ± sensory de cits ± motor weakness ± decreased tendon re exes	X-ray of cervical spine (AP, lateral, and open-mouth view) May need CT/MRI	Non-opioid analgesics NSAIDs Opioids for a limited time
IV	Neck pain/sti ness/ tenderness + dislocation/ fracture ± spinal cord injury	CT, MRI, myelography, discography	Non-opioid analgesics NSAIDs Opioids Immediate referral to spinal surgeon

Source: Data from Spitzer, W., O., *et al.* (1995). Scienti c monograph of the Quebec Task Force on Whiplash Associated Disorders: rede ning 'whiplash' and its management. *Spine*. 20(8):8S–58S.

Acute whiplash injury manifests with symptoms for up to 4 weeks; in subacute whiplash, symptoms persist until 12 weeks, beyond which the condition is termed chronic WAD

Mechanism of injury

(See Fig. 23.4.1.)

WAD usually occurs in rear-end, low-impact collisions

The vehicle occupant's trunk is forced back on the seat, with neck hyperextension, followed by forward recoil

The risk is higher in people with thinner necks (women) or short necks, and if the collision is with a heavy vehicle

Cervical facet joints (especially C2/3 and C5/6) have been implicated as the main source of whiplash pain

Treatment

Acute whiplash—physiotherapy and manipulation improve neck pain and ROM. Hot and cold packs, hydrotherapy, traction, US, laser therapy, short-wave diathermy, TENS, and acupuncture may help. NSAIDs, amitriptyline, diazepam, epidural LAs, and steroids have variable bene ts

Subacute whiplash injury—postural training, eye xation exercises, and psychological support help more than physical therapy alone. Multidisciplinary functional rehabilitation programmes may reduce pain and catastrophizing

Chronic WAD—RF denervation of the cervical facet joints has shown reasonable bene t. Facet steroid injections, muscle Botox® injections, and traction may provide short-term bene t. Multimodal rehabilitation programmes combining physical and cognitive behavioural therapies result in better outcomes, compared to physical therapy alone

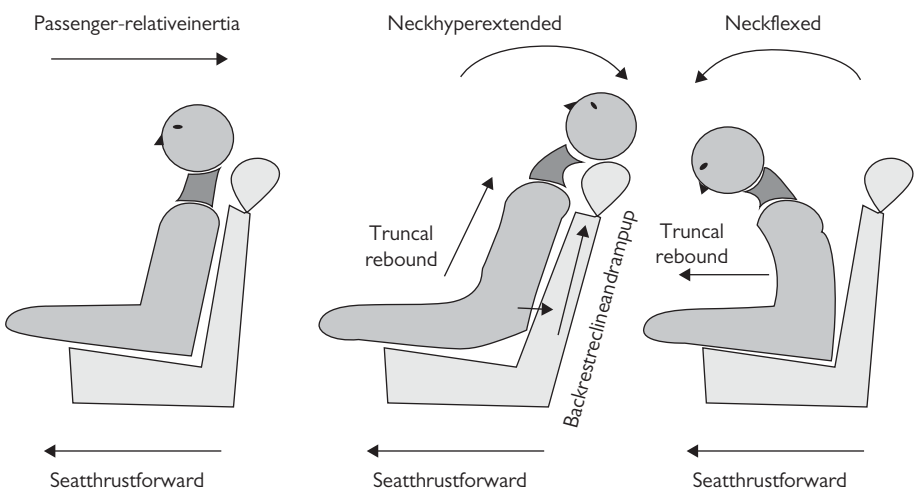


Figure 23.4.1 Mechanism of injury

Reproduced with permission from Tameem, A., Kapur, S., and Mutagi, H. (2014). Whiplash injury. *Continuing Education in Anaesthesia Critical Care & Pain*, 14(4);167–170. https://doi.org/10.1093/bjaceaccp/mkt052

Grade III or IV WAD—may require surgical intervention, including cervical fusion or subacromial decompression

Medico-legal factors

The UK has the highest incidence of WADs in Europe and make up three-quarters of all vehicle insurance claims

Compensation-driven litigation culture has led to a rise in reported WADs

Pain and disability can persist once chronic WAD has developed, even after receipt of compensation

Around 40% of patients su er from symptoms of WAD beyond 3 months (chronic whiplash) and up to 5% of patients develop persistent disability

Further reading

1. Spitzer WO, Skovron ML, Salmi LR, et al. Scienti c monograph of the Quebec Task Force on Whiplash Associated Disorders: rede ning 'whiplash' and its management. Spine 1995;20(8):8S–58S
2. Tameem A, Kapur S, Mutagi H. Whiplash injury. Contin Educ Anaesth Crit Care Pain 2014;14(4):167–70. https://doi.org/10.1093/bjaceaccp/mkt052

23.5 Shoulder pain

Introduction

Pain arising from anatomical structures in the shoulder or described as such; also consider referred pain from nearby joints, the cervical plexus, and the cervical spine

Very common—up to 66% lifetime prevalence, 60% incidence in women

There is a correlation between atherosclerosis, diabetes, and shoulder pain

Anatomy

Three bones:

- Head of the humerus
- Glenoid fossa (scapula)
- Clavicle

Three joints:

- Glenohumeral joint between the humerus head and the glenoid fossa (scapula).The glenoid labrum (cartilage) increases the depth of the glenoid fossa to promote stability of the joint
- The ACJ between the acromion (scapula) and the clavicle
- Sternoclavicular joint (SCJ) between the sternum and the clavicle

Three bursae:

- Subacromial–subdeltoid bursa deep to the deltoid and coracoacromial arch, super cial to the supraspinatus tendon
- Subcoracoid bursa located anterior to the subscapularis muscle and inferior to the coracoid process
- Subscapular bursa between the subscapular tendon and the joint capsule

Joint capsule:
- From the anatomical neck of the humerus to the border of the glenoid fossa, lined by synovial membrane

Five ligaments:
- Glenohumeral ligaments (superior, middle, and inferior)
- Coracohumeral ligament
- Transverse humeral ligament
- Coracoclavicular ligament
- Coracoacromial ligament which forms the coracoacromial arc

Muscles:
- Deltoid muscle:
  - Innervated by the suprascapular nerve (C5)
  - Abducts the arm 30–90°
- Four rotator cu muscles:
  - Supraspinatus muscle
    - Innervated by the suprascapular nerve (C5)
    - Abducts the arm 0–30°
  - Infraspinatus muscle:
    - Innervated by the suprascapular nerve (C5)
    - Externally rotates the arm 90%
  - Teres minor muscle:
    - Innervated by the axillary nerve (C5)
    - Externally rotates the arm 10%
  - Subscapularis muscle:
    - Innervated by the subscapular nerve (C5–6)
    - Internally rotates the arm 90%

Nerve supply from the suprascapular, axillary, subscapular, and lateral pectoral nerves

Movements:
- Shoulder joint is a ball-and-socket joint (synovial joint), covered with hyaline cartilage
- Movements: extension, exion, abduction, adduction, external and internal rotation

Joint stability from rotator cu muscles, the glenoid labrum, ligaments, and biceps tendons

Pathophysiology

Tendon in ammation, tear, or degeneration (bursitis or tendinitis)

Joint instability

Arthritis (septic, OA, autoimmune)

Trauma causing fracture, joint dislocation, and rupture of ligament

History

Sudden versus chronic onset, history of trauma, previous dislocation, rheumatological symptoms, including joint swelling, morning sti ness, lethargy, weight loss, loss of appetite, fever, and malaise. Occupation, hobbies, and sports

Examination

Inspection:
- Posture, scar, asymmetry of shoulder girdle, swelling, wasting

- Winging of the scapula when arms stretched against the wall (can be due to an injury of the long thoracic nerve)
- Performance of a functional task (e.g. take o /put on shirt)

Palpation:

- Temperature, areas of tenderness, and allodynia (static mechanical, deep somatic, thermal)
- Bones and joints:
  - Clavicle, humerus, scapula, SCJ, and ACJ
- Muscle and tendons:
  - Rotator cu , biceps, triceps, deltoid, pectorals, neck muscles
  - Tone (increased in UMN and decreased in LMN lesions)

Movement active, passive, and against resistance:

- Flexion (150°), extension (40°), abduction (180°), adduction (30°), external rotation (80°), internal rotation (reach T6 spinal level)
- Power grade 0 (none) to 5 (normal)—Medical Research Council scale for muscle power
- Palpate for joint crepitus and assess joint instability
- Dynamic mechanical allodynia

Sensation, re exes, and coordination of upper limbs

Rotator cu muscles, tendons, and glenohumeral stability:

- Rotator cu muscles
  - Supraspinatus muscle (empty can test): arms at 90°, with elbows extended, full pronation, and internal rotation of the forearm. Thumbs are pointing down as if the patient were pouring liquid out of a can
  - Infraspinatus muscle and teres minor: externally rotate the arm against resistance
  - Subscapularis (belly o sign): patient rests hands on the abdomen and examiner tries to pull them away
- Rotator cu tendons—impingement tests:
  - Neer's test: the scapula is stabilized with the thumb pointing down and the arm is passively exed
  - Hawkin's test: arms forward at 90°, elbows exed, forceful internal rotation of the shoulder
- Glenohumeral stability with the apprehension test:
  - Patient sitting or supine, with shoulder 90° abducted. Anterior pressure to the humerus, externally rotating the shoulder

Cervical spine and elbow joint examination

Investigations

Psychometric questionnaires (see 30.1 Psychometric assessments, p. 613). Shoulder Pain and Disability Index Questionnaire measures pain and disability in patients with shoulder pain

Plain X-ray—fracture, dislocation, arthritis

US—diagnostic for tendinitis and joint e usion

MRI—soft tissue assessment, injury to ligaments and tendons

EMG and NCS—can help identify the location of an injury (brachial plexus, peripheral nerve, or spinal cord)

Di erential diagnosis

Primary shoulder pathology

Shoulder joint/capsule—dislocation, trauma, arthritis degenerative, immune related or other cause, frozen shoulder, avascular necrosis

Rotator cu —tear, impingement

Bursa—subacromial bursitis

Shoulder instability—recurrent dislocation, trauma, collagen disorder

Referred pain

Cervical origin—radicular and referred pain from cervical spondylosis, disc degeneration/prolapse, facet joint disease

Pain from the diaphragm and of visceral origin such as angina and biliary colic

Systemic disorders such as bromyalgia and polymyalgia rheumatica

Treatment

Vast majority of shoulder problems are treated conservatively initially, mainly with simple analgesics and physiotherapy

Physical, pharmacological, and psychosocial interventions, as per chronic pain management principles, are used to preserve and promote shoulder function

Surgical interventions

Shoulder arthroscopy

Manipulation under anaesthesia for frozen shoulder

Arthroscopic or open rotator cu repair

Shoulder joint replacement

Pain interventions

Further details about procedures are covered elsewhere in the book. Performed using either the landmark technique, X-rays, or US guidance:

Nerve block and/or PRF treatment:

- Suprascapular block—pathologies of the glenohumeral joint
- Axillary nerve block—pain in the regimental badge area on the arm

Subacromial bursa injection:

- Subacromial impingement, rotator cu disorder, adhesive capsulitis

Glenohumeral joint injection:

- Glenohumeral arthritis, adhesive capsulitis, labrum tears

Additional information

60% patients recover by 1 year from all causes of shoulder pain, but has a tendency to recur

Adhesive capsulitis (most patients completely recover):

- First phase (2–9 months): the pain is very prominent
- Second phase (4–12 months): reduced range of motion is more prominent than pain
- Third phase (5–24 months): gradual recovery

Further reading

1. Gray M, Wallace A, Aldridge S. Assessment of shoulder pain for non-specialists. BMJ 2016;355:i5783

23.6 Carpal tunnel syndrome

Introduction

The carpal tunnel is a narrow canal on the volar aspect of the wrist, covered by the exor retinaculum and bound on three sides by the carpal bones distally. It contains exor tendons in their sheaths, the median nerve, blood vessels, and lymphatics

Compression of the median nerve in the carpal tunnel results in carpal tunnel syndrome

Aetiology

Idiopathic in >50% of patients

Associated conditions: RA, diabetes, obesity, repetitive strain injury, pregnancy, CMT syndrome type 1, amyloidosis, hypothyroidism

History

Pain, numbness, and paraesthesiae on the thumb, index, middle nger, and lateral half of the ring nger

The pain may extend to the forearm

Reduced grip and dropping items from the hand are common

More frequent in women

Examination

Sensory de cits of the thumb, index, middle nger, and lateral half of the ring nger

Muscle weakness and atrophy of the thenar eminence in later stages

Positive Tinel's sign and Phalen's test

Investigations

Investigations to identify the underlying cause

NCS

EMG

Diagnosis

Diagnosis mostly from clinical symptomatology. Other diagnoses to consider include cervical radiculopathy, arthritis, diabetic neuropathy, or other causes of peripheral neuropathy

Treatment

NSAIDs, paracetamol, and physiotherapy

Carpal tunnel decompression surgery—better outcomes than steroid injections

Treatments with lower evidence:

- Steroid injections
- Neutral wrist splints, especially at night, but prolonged use may weaken the muscles
- Others: acupuncture, US, yoga, and carpal bone mobilization

Further reading

1. Stevens JC, Beard CM, O'Fallon WM, et al. Conditions associated with carpal tunnel syndrome. Mayo Clin Proc 1992;67:541–8

23.7 Low back pain

De nition

Low back pain is an imprecise term used to describe varying combinations of pain, muscle tension, and sti ness below the costal margins and above the inferior gluteal folds

With or without radicular pain

Prevalence

Low back pain is the most common chronic pain complaint

Lifetime prevalence is 60–80% in industrialized countries, with 1-year prevalence of 15–45%

Prevalence increases from age 30 to 60, then stabilizes

Good prognosis of acute low back pain—90% of episodes resolve

Prevalence of chronic low back pain in adults in a European survey: 18%

In 2009, there were 1.6 million people with chronic back pain in the UK and the cost of back pain to the economy was £12.3 billion

Risk factors

Obesity, smoking

Sedentary lifestyle

Heavy physical work (repetitive lifting, twisting)

Prolonged standing in an awkward posture

Lower socioeconomic status

Depression

Pathophysiology

The human spine accumulates degenerative ('wear and tear') changes from early adulthood onwards

Facet joints and SIJs accumulate degenerative changes and can become osteoarthritic

Discs with acute tears can leak nucleosus pulposus gel, which is in ammatory outside the disc

Disc degeneration can lead to abnormal stress and in ammation in the adjacent vertebral endplates

Pain from any cause in the spine promotes muscular tension and altered postural and movement patterns, which contribute to further pain

Aetiology

Facet joint OA (arthropathy/degeneration)

SIJ OA (arthropathy/degeneration)

Discogenic back pain (from disc degeneration sequelae)

'Myofascial'—muscle motor pattern dysfunction with muscle tension and fatigue

Spondylolisthesis—associated facet joint OA and myofascial pain

Lumbar radicular pain—disc degeneration, stenosis, post-surgery

Central sensitization—central ampli cation seen in chronic pain

Less common causes of back pain that need to be kept in mind and excluded are:

- Osteoporotic and traumatic fractures
- Malignancy (e.g. myeloma, prostate cancer)
- Infection: frank infection is rare, unless a complication of surgery, but discitis can occasionally occur through blood-borne spread of bacteria
- There is some evidence that very low-grade infection of discs may be implicated in some cases of low back pain symptoms

Diagnosis

Exclusion of red and yellow flags

Red flags trigger a more detailed history and examination ± investigations to avoid missing uncommon, but serious, underlying disease

Red flags: severe pain, night pain, thoracic pain, fever, unexplained weight loss, history of carcinoma, immunocompromise, history of long-term corticosteroids, progressive neurological deficit, disturbed gait, bladder or bowel sphincter dysfunction, saddle anaesthesia, age of onset <20 years or >55 years

Yellow flags (psychosocial factors indicating long-term chronicity and disability, interventions less likely effective, multidisciplinary treatment (MDT) approach needed):

- Catastrophization—belief that back pain is harmful, progressive, and potentially severely disabling
- Fear avoidance behaviour and reduced activity levels
- Expectation that passive, rather than active, treatment will be beneficial
- Tendency to depression, low morale, and social withdrawal
- Social or financial problems

Distribution and pattern of pain

Axial pain versus radicular pain

A useful way to look at low back pain is to determine if the pain has an axial or a radicular pattern

Axial pain

- Adjacent to the spine
- Usually associated with paraspinal muscle tension and tenderness, with any spread into limbs being proximal and limited
- Axial pain suggests spinal MSK drivers, including facet joint and SIJ arthropathy, lumbar disc degeneration with vertebral endplate inflammation, and muscle and ligament inflammation/injury

Radicular pain

- Travels down a limb or around the thorax in a band consistent with a nerve root distribution
- Result of nerve root inflammation/ischaemia/injury
- Usually with neuropathic features

Axial discogenic back pain

- Lumbar disc degeneration is normal as we age
- Discs do not have internal nerves and most degenerations are not painful
- Discogenic axial pain is worse with loading of the discs (flexion, sitting, and activities that increase disc pressure)
- Mechanisms whereby disc degeneration may produce axial pain:

Leakage of nucleosus pulposus (rich in pro-in ammatory phospholipase A2) into adjacent structures

Peripheral ingrowth of nociceptive nerves accompanying granulation tissue into damaged discs

Possibly associated low-grade disc and vertebral endplate infection in some cases

Altered mechanical loading on adjacent structures

Mixed presentations

Elements of both axial and radicular pain present

May be due to having both axial and radicular pathology

Can also be due to severe 'axial' pathology pain being referred down a limb (e.g. in severe SIJ arthropathy)

With primary radicular pain, secondary muscle tension and guarding of the spine can cause associated axial pain

Neurogenic claudication pain as a special case

Usually seen in older patients

Spinal nerve or cauda equina blood supply is limited by stenosis (spinal canal narrowing) or brosis following surgery, and ow cannot increase to meet the demands of activity

A complaint of radicular symptoms in one lower limb with activity may be encountered with narrowing of one side of the spinal canal (lateral recess stenosis)

In central lumbar spinal canal stenosis, the typical presentation is one of low back pain and bilateral lower limb heaviness and pain with walking—especially uphill

Walking distance becomes limited and there is a tendency to stoop when walking

Consider referral to spine surgery team

Examination

Gait, posture, deformity, surgical scars, use of supportive braces, skin changes (e.g. from hot water bottle)

Range of movement, muscle tone, tenderness

Reduced straight leg raise, positive neural stretch tests (slump test)

Neurological de cit (sensory, motor, re ex impairment), distribution of paraesthesiae or sensory loss, reduced ankle and great toe dorsi exion, knee and ankle re exes

Test dermatomal (sensation) and myotomal (motor weakness) distribution of symptoms, which usually correlate with speci c nerve roots for radicular pain (e.g. pain on top of the foot and foot drop - L5 nerve root) (see 1.4 Dermatomes and myotomes, p. 14)

Pain behaviour (avoidance, guarding, inconsistencies)

Investigations (if appropriate)

X-ray—rarely indicated (trauma, osteoporotic or malignant vertebral fractures, scoliosis, dynamic spondylolisthesis views)

CT and MRI—not essential in non-speci c low back pain, but indicated in radicular pain symptoms (disc degeneration, facet joint degeneration, foraminal narrowing, nerve root compromise, spinal canal stenosis, vertebral collapse/fracture) and other red ag presentations

DEXA scan (to assess for osteoporosis)

Treatment

Education, reassurance (the majority of acute low back pain exacerbations improve, and patients should be educated that back pain is common and degenerative spinal changes are normal, and reassured that their spine is stable and will bene t from remaining active)

Patients should be considered holistically (biopsychosocial model)

Emphasize and encourage positive lifestyle changes (e.g. maintenance of physical condition, avoidance of smoking, and weight control)

Simple analgesics if they prove useful: paracetamol, NSAIDs (muscle relaxants for acute spasms should only be prescribed for a short and limited time)

Physiotherapy may be o ered (gentle and frequent exercising and stretching)

Axial low back pain

When chronic axial low back pain is moderate to severe and refractory to the above conservative measures and red ag exclusion has been made, then interventional techniques may be considered

Axial back pain should be regarded as 'back pain for investigation' as the contribution of any interventional target in driving axial pain is unclear until it is tested

Radicular pain

Radicular pain is usually due to nerve root irritation

If radiculopathy is present (numbness/weakness in addition to pain) or if the pain is persistent, then MRI of the lumbo-sacral spine is indicated prior to considering targeted nerve root (transforaminal epidural injection) or lumbar epidural injection

Surgery in the case of refractory compressive radiculopathy

Axial discogenic back

Education and reassurance (resume normal activities as soon as possible)

Encourage return to work (manual handling and lifting may be needed), occupational health

Interventional treatments for discogenic pain (none has strong evidence):

- Injection of discs with steroids, sclerosants, methylene blue, or stem cells
- Disc cauterization
- Disc replacement surgery, spacer device surgery to o oad the disc, spinal fusion surgery
- Antibiotics in the presence of Modic type 1 vertebral endplate changes
- SCS

Further reading

1. Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of e cacy. Eur Spine J 2013;22(4):697–707
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23.8 Lumbo-sacral transitional vertebrae

Introduction

Relatively common congenital spinal anomalies

Refers to vertebrae with intermediate morphological features

Could take the form of either an assimilation of the fth lumbar vertebra to the rst sacral vertebra *(sacralization)* or a transition of the rst sacral vertebra to assimilate the lumbar vertebra morphology (*lumbarization*)

An association with back pain was rst described by Mario Bertolotti in 1917

It alters the numerical labelling and counting of the vertebra; hence, in cases of lumbarization, it is *L6/S1* and in sacralization *L4/S1*

Incidence

Generally reported to be 4–30%

Aetiology

Not completely understood, but genetic factors are believed to be very important

Clinical signi cance

Although the evidence is lacking, it is frequently associated with degenerative disc disease or herniation, spinal central canal or foraminal stenosis, and facet joint arthrosis

Potential association with back pain

Could lead to errors of identifying the correct level during surgery or pain interventions

Investigations

Plain radiographs: AP and lateral of the lumbo-sacral spine. This can be combined with an AP and 30° cranial tilt lm

CT scan

MRI scan

Castellvi diagnostic classi cation (1984)

Type 1. Dysplastic TP—unilateral (1a) or bilateral (1b) TP (>19 mm wide)

Type 2. Incomplete sacralization/lumbarization—unilateral (2a) or bilateral (2b) enlarged TP pseudarthrosis with the adjacent sacral ala

Type 3. Unilateral (3a) or bilateral (3b) fused completely with the adjacent sacral ala

Type 4. Mixed—type 3a and 2a on each side

Treatment

Physical, pharmacological, psychological, and psychosocial interventions as per chronic pain management principles

Surgical and interventional pain management treatments—unclear which of these treatments is more e cacious. Some of the available treatments include:

- Injection of LA and steroids into the pseudarthrosis or contralateral facet joint
- RF ablation of the nerve supply after a positive diagnostic block
- Surgical resection of a partial TP or an anomalous articulation

Further reading

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23.9 Failed back surgery syndrome

Introduction

FBSS is usually diagnosed if pain recurs or gets worse 6 months after technically adequate spinal surgery, although variations exist in the description of this syndrome

The aetiology is complex, with normally a mixture of nociceptive, neuropathic, and sympathetic contributors

Around 30% of patients experience persistent or recurrent pain following technically adequate spinal surgery, which is a signi cant clinical and economic burden

The role of certain surgeries such as spinal fusions is controversial, with a mixture of critical and supportive expert publications

Factors associated with positive pain outcomes in spinal surgery

The patient has realistic expectations and understands the surgical risks

Medically t and motivated to get better

Has had appropriate conservative management

Surgery not delayed in cauda equina syndrome, potential unstable fractures, spinal malignancy (primary or metastatic), infections (discitis, osteomyelitis), signi cant spinal canal stenosis, and defects that worsen with time such as scoliosis in young patients

Factors associated with poorer pain outcomes in spinal surgery

Unrealistic expectations by patient or clinician

Surgery performed for pain relief in the absence of a clear pathology amenable to surgical correction

Psychological factors:

- Personality traits associated with anxiety, worry, agitation, and anger
- Cognitive factors such as low self-e cacy, poor pain-coping skills, catastrophizing, sense of injustice
- History of abuse (sexual, physical, verbal, neglect)

Mental health conditions not optimized such as depression, anxiety, substance use disorders, and others

Social factors: unemployment, ongoing litigation or disability bene t application, relationship di culties, con ict with employer/insurance, poor working conditions, negative in uence by signi cant others such as family

Medical factors: physically deconditioned, smoking, poor nutrition, high BMI, older age, multiple medical comorbidities, opioid-tolerant

Causes of failed back surgery syndrome

Surgical procedure was probably not indicated

Other pathologies/pain generators that are contributing to the pain were not addressed during the surgical procedure

Surgical complication such as epidural brosis at surgical site (common), trauma to nerve roots, or other complications

Recurrence of pathology or development of a new pathology after the surgery such as disc herniation/herniation at adjacent level

Pre-existing irreversible nerve damage caused by disc herniation/sequestered disc fragment/cauda equina syndrome

Treatments

Treatment is controversial

Exclude red ags

Repeat surgery may not produce the expected improvement in pain relief

Detailed biopsychosocial assessment with a multidisciplinary team approach, including patient education, exercise, physiotherapy, and psychological treatments are essential

Trial of pharmacological agents for neuropathic pain (antidepressants, gabapentinoids, see Chapters 9 and 10.)

Interventional pain medicine has limited evidence of e cacy. However, some speci c patients bene t from speci c interventions such as ESIs, sacroiliac or medial branch blocks ± RF denervations, epiduroscopy, and adhesiolysis

There is evidence to support SCS for neuropathic pain in FBSS

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23.10 Spondylolysis

Introduction

Spondylolysis refers to an osseous defect of the pars interarticularis (isthmus) of the vertebral arch

It is derived from the Greek words *spondylos* (vertebra) and *lysis* (defect)

Incidence

Reports vary from 4–6% to 6–8% of the general population

Could reach a staggering 63% in participants of certain sports

With spondylolisthesis, it is the most common reported cause of low back pain in children and adolescents older than 10 years

Anatomy

Unilateral or bilateral (more common)

The pars interarticularis constitutes the junction between the laminae, articular facets, and the pedicles of the vertebra

Bone formation/osteophytes (made of osseous, brous, and cartilaginous tissues) in vertebral discs, joints (facet and uncovertebral), and vertebral bodies, which can result in:

- Foraminal neural narrowing, nerve root compression, and radicular symptoms from the bone growth at facet and uncovertebral joints
- Compression of the spinal cord and myelopathy from changes in vertebral body margins and the posterior longitudinal ligament

In bilateral cases, the upper vertebra can slide over the lower one (spondylolisthesis) or posterior neural arch displacement

More commonly found in the cervical/lumbar spine than in the thoracic spine (most likely because the thoracic spine is more rigid)

In lumbar cases, L5 is a ected in 85–95%, followed by L4 in 5–15%

Pathophysiology

Is not completely understood. Aetiology is multifactorial:

- Genetic: high incidence amongst family members—up to 69% of cases
- Ageing is a very important factor
- Trauma, mechanical stress, fatigue fractures from repetitive mechanical loading
- Repetitive spinal rotation/ exion/extension movements
- Vertebral discs lose height and water content, with weakening of the annulus brosus

It is hypothesized that a combination of the above factors results in increased mechanical stress in the vertebral endplates, facet joints, and uncovertebral joints. This leads to the development of osteophytes, hypertrophy of the ligaments, and osseous structures

Strong association with spina bi da occulta

Clinical picture

Red ags need to be excluded

Most cases are asymptomatic, only accidentally discovered radiologically

Can develop gradually over time, with are-ups following particular events or movements, after an acute event, or with no precipitating factor/explanation

Symptomatic cases tend to complain of focal mechanical low back pain radiating into the buttocks. This can particularly pose a problem in young athletes

Normally aggravated by spinal hyperextension

Patients sometimes complain of radicular pain:

- Atypical radicular pain: position-dependent and not associated with neurological signs
- Typical radicular pain: neurological symptoms and signs secondary to neural compression

Physical examination may reveal:

- Exaggerated lumbar lordosis, in addition to tightness of the hamstrings, although the exact explanation for this is unknown
- Neurological signs of radiculopathy
- Evidence of central sensitization

Investigations

Plain radiographs: pars defect appears as an area of lucency in the pars interarticularis, resembling a break in the neck or 'collar' of the 'scottie dog'. However, detection of the defect may be di cult and require multiple views

SPECT: more sensitive than plain X-rays in detecting the lesions

CT scan: more sensitive than plain X-rays. It is considered by many to be the imaging modality of choice

MRI

Often >1 modality is used

Treatment

Physical, pharmacological, psychological, and psychosocial interventions as per chronic pain management principles

Development of active pain self-management strategies such as pacing, goal setting, thought resolution, exercise, management of flare-ups, etc.

Some patients benefit from a spinal brace

Surgery normally considered after failure of conservative management after 6 months in specific patients where surgery can correct anatomical deficits. Some of the procedures that can be done include:

- Spinal fusion—sometimes an uninstrumented fusion of L5/S1 with an autogenous iliac crest bone graft is performed
- Repair of the pars defect at L4 or above can be indicated in children and adolescents
- Spinal decompression

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23.11 Sacroiliac joint pain

Definition

Pain localized in the region of the sacroiliac joint (SIJ), reproducible by stress and provocation tests, and reliably relieved by selective infiltration of the SIJ

Prevalence

16–30% amongst patients with axial low back pain (depending on the use of diagnostic criteria)

Anatomy—introduction

SIJs are the largest joints in the body, and they join the sacral spine to the pelvis

The upper part of the joint is fibro-cartilaginous, and the lower part is a synovial joint

SIJs bear heavy loads when we are standing and walking

SIJs normally have very limited movement

Their function is to combine stability with a cushioning effect

They may become painful due to degenerative change or injury

Pain is felt at the lumbo-sacral level in the region of the joint and typically spreads into the buttock and thigh

Aetiology

SIJ arthropathy is involved in around 5–10% of chronic low back pain

SIJ arthropathy is usually due to degenerative/osteoarthritic processes

Less common causes are inflammatory arthritis, including ankylosing spondylitis and gout

Risk factors for SIJ instability: younger age, pregnancy, hypermobility, trauma

Risk factors for SIJ arthropathy: leg length discrepancy, abnormal gait, trauma, scoliosis, lumbar fusion surgery with fixation of the sacrum (prevalence of 32–33% demonstrated with SIJ blocks), pregnancy, heavy physical exertion

History

Pain in gluteal region (94%)

Referred pain to lower lumbar area (72%), groin (14%), upper lumbar area (6%), abdomen (2%), lower limb (28%), and foot (12%)

Examination

SIJ instability can present with severe lumbo-sacral pain and even with a sciatica type of pain

Large forces are needed to stress the joint due to its size and immobility

Tests: (1) stressing of the SIJ with distraction (antero-posterior pressure on ASIS in prone position); (2) thigh thrust; (3) Faber test; (4) compression (pressure on iliac crest in lateral position); and (5) Gaenslen's test. Three out of five positive tests indicates likely SIJ pathology (specificity of 79% and sensitivity of 85%). A single test is of little value

Imaging

Indicated when red flags are present (X-ray, CT, MRI, bone scan)

Differential diagnosis

Spondyloarthropathy (ankylosing spondylitis, reactive or psoriatic arthritis)

Lumbar nerve root compression

Lumbar facet joint arthropathy

Hip pain

Endometriosis

Myofascial pain

Piriformis syndrome

Treatment

Conservative

Physiotherapy and manipulation (posture and gait disturbances)

Immuno-modulators in rheumatological disorders (ankylosing spondylitis)

Pain interventions

NICE Guideline 59 does not make specific reference to SIJ procedures

IASP criteria support the confirmation of diagnosis by successful injection

Injection of the SIJ with LA and steroid is supported by low to moderate evidence—can be carried out under X-ray or US control (see 18.2 Sacroiliac joint block and radiofrequency denervation, p. 340)

RF denervation of the SIJ:

Supported by moderate evidence

Innervation of the SIJ is more complex and variable than that of the facet joint, and several different techniques are described

The anterior contribution to innervation of the joint cannot be lesioned

The majority of the nerve supply to SIJs is from the lateral branches originating from S1 and S2, but branches of L5, L4, S3, and S4 may contribute

When instability is a major problem, SIJ injections and denervations do not produce lasting pain relief and prolotherapy (injections of brosing solutions into and along the joint ligaments) and surgical xation may be considered

Further reading

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23.12 Coccygodynia

De nition

In ammation or displacement of the coccyx (tailbone) presents with pain and tenderness at the tip of the tailbone

Incidence

Female:male ratio = 5:1

Female coccyx is longer and most posteriorly placed, and parturition predisposes to a high incidence

70% of traumatic births cause coccygeal joint injury

Other risk factor: high BMI

Anatomical correlation

Coccyx = nal segment of the vertebral column

3–5 coccygeal vertebrae are present

Attached to the sacrum at the sacro-coccygeal junction

It is one leg of the weight-bearing tripod along with the ischial tuberosities in the sitting position

Ligamentous attachments: sacro-coccygeal, sacro-spinal, sacro-tuberous, and anococcygeal ligaments

Muscles: levator ani, gluteus maximus, gluteus medius, gluteus minimus, coccygeus muscle, and other deep gluteal muscles, such as obturator internus and piriformis, can refer pain to the coccyx region

Causes

Acute trauma

Traumatic parturition

Repetitive stress injury such as cycling

Incorrect sitting position

Motor sports

Diagnosis

Mostly history: history of trauma, dull and deep achy pain in coccygeal region
Detailed history to exclude di erential diagnoses listed below
Chronic pelvic pain can be associated with coccygodynia; detailed psychosocial and sexual history is mandatory
Manual examination (including per rectal examination)
X-ray: plain X-ray, lateral view to exclude fracture and dislocation; dynamic radiology can be used in di cult cases
MRI: mainly to rule out sinister pathology

Di erential diagnosis

Infection: shingles, osteomyelitis, local infection
CNS tumours, cysts
Malignancy: primary and secondary
Referred pain: pelvic structures, such as rectum and lower part of the colon, urogenital structures, and lumbar disc herniation
Nerve entrapments causing referred pain (cluneal nerves)

Treatments

Multidisciplinary and multimodal approach is crucial for success of therapy as for other chronic pain conditions

Conservative management

Up to 90% of cases get better with conservative treatment and simple analgesics
Adapting sitting position
Coccyx cushion
Physiotherapy for pelvic oor structures and exercise
Therapeutic US therapy
Acupuncture
Heat/cold application
TENS
CBT and other psychotherapies

(Some of these treatments have limited evidence.)

Pharmacological

Simple analgesics, especially NSAIDs if there is no contraindication

Interventions

LA and steroid injection under X-ray or US guidance (60–85% success rate)
Caudal block
Ganglion impar block
RF or PRF denervation or pulsed RF of sacral nerve roots

Neuromodulation techniques

Only in selected cases (currently limited evidence as it is an emerging treatment option and many are case series)
TENS
Peripheral eld stimulation

PNS
SCS

Surgical

Surgical removal (coccygectomy) is not recommended routinely due to high risk of post-surgical pain and brosis and only moderate long-term e ect

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23.13 Piriformis syndrome

De nition

'*Pain in the buttock and posterior thigh due to myofascial injury of the piriformis muscle itself or dysfunction of the sacroiliac joint or pain in the posterior leg and foot, groin and perineum due to entrapment of the sciatic or other nerves by the piriformis muscle within the greater sciatic foramen, or a combination of these causes*' (ISAP)

Incidence

5–8% of low back pain

Anatomy of piriformis muscle

Origin: antero-lateral surface of the sacrum between the anterior sacral foramina, runs laterally and inferiorly through the greater sciatic foramen

Insertion: upper margin of the greater trochanter of the femur

Function of muscle

Adductor of exed thigh and external rotator of extended hip

Adjacent structures

Sciatic nerve, superior gluteal nerve, posterior femoral cutaneous nerve

Nerves to superior and inferior gamelli, obturator internus, quadratus femoris, and gluteus maximus, medius, and minimus

In 88% of the times, the sciatic nerve passes below the muscle. Sometimes it passes between a split muscle or is divided with one division passing above and the other below the muscle or through the muscle

Pathophysiology

Pathology and dysfunction of the piriformis muscle can cause low back pain, buttock pain, and sciatica because of muscle spasm and compression of the sciatic nerve

Predisposing factors

Trauma (50%):

Direct injury, prolonged sitting, sport injuries, e.g. cycling, dancing

Obesity

Pregnancy

Cerebral palsy (increased muscle tone)

Limb length discrepancy

Abnormal posture

Diagnosis

Symptoms and signs: ipsilateral (usually) pain in the buttock, lower back, and posterior thigh, occasionally radiating below the knee, dyspareunia and labial pain (females), scrotal pain (males), painful bowel movements

Aggravating factors: walking, prolonged sitting

Examination/tests:

Tenderness to palpation over the muscle

Lasegue's sign: pain and tenderness in the greater sciatic notch on voluntary exion, adduction, and internal rotation of the hip

Pace's sign: pain and weakness on resisted abduction of the hip with the patient seated

Freiberg sign: pain on forced internal rotation of the extended thigh

Investigations: CT and MRI may show enlargement of the piriformis. EMG may show delay in the H re ex on exion, adduction, and internal rotation (FAIR) of the hip

Treatment

Conservative: physical therapy, in combination with analgesics, anti-in ammatory drugs, and muscle relaxants

Treatment of a correctable cause such as posture, limb length discrepancy, weight reduction, and avoiding precipitating factors

Injection treatment:

LA and steroid into the muscle

BTX-A (100 IU) into the muscle if there is a transient improvement of symptoms with steroid and LA

Injections performed under uoroscopy guidance, but US- and CT-guided injections are more accurate

Surgery:

Excision, thinning, or tendon release of the muscle may be considered for severe refractory cases

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23.14 Greater trochanteric pain syndrome

Introduction

Regional pain syndrome with chronic intermittent pain around the bony prominence over the lateral aspect of the hip (greater trochanter region)

Previously known as trochanteric bursitis—now thought that the bursa perhaps has a smaller role and in ammation is not always present

Pathophysiology

Greater trochanter provides lubrication and cushioning to tendons, allowing muscles to ex and extend. In ammation or trauma (acute or recurrent) in muscles, tendons, fascia, or bursae is associated with this condition

More common in women aged 40–60 years

Common associations:

- Gait disturbances and postural abnormalities secondary to sacroiliac, spinal, and muscular disorders
- Low back pain, knee pain, RA, and bromyalgia
- Previous hip surgery

Risk factors for a poorer outcome: older age, poorly controlled acute pain, long duration of pain, greater movement restriction or functional impairment

History and examination

Lateral hip pain, possible radiation of pain to the infero-lateral aspect of the thigh

Pain aggravated on hip movement

Spasticity in the muscles and tendons attached to the greater trochanter

Pain on palpation of the greater trochanter (point tenderness)

Positive Trendelenburg test

Rule out an infected bursitis: tender palpable mass, warmth, redness, or oedema

Investigations

It is a clinical diagnosis. Imaging and/or blood tests are warranted if suspicion of fracture, hip arthritis, avascular necrosis of the head of the femur, malignancy, tendon tears, or tendinopathies (e.g. gluteus medius tendinopathy)

Di erential diagnosis

Sports hernia

Infection of the bursa or surrounding structures

Pain referred from the hip and lumbar area (e.g. lumbar nerve root compression), abdomen, or other surrounding structures

Treatment

Reassure: 90% recover with conservative measures

In the acute phase, avoid repetitive hip movements or lying on the a ected hip, ice packs (apply for 10–20 minutes several times a day), simple analgesics (paracetamol or NSAIDs), and weight reduction (if appropriate)

Physiotherapy and correction of underlying gait disturbances

If pain persists, consider:

Intra-bursa injections of LA and steroid (landmark technique or under X-ray or US guidance)

Other options: TENS, shockwave therapy, surgical bursectomy (very rarely performed)

Refer to rheumatologist or orthopaedic surgeon if in doubt with diagnosis, persistent pain despite maximal medical treatment, suspected infection, previous hip problems (hip surgery or fracture femur)

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23.15 Plantar fasciitis

De nition

Persistent heel pain resulting from chronic overuse, or degenerative and reparative process a ecting the origin of the plantar fascia at the distal calcaneum

Incidence

11–15% of foot symptoms, and 80% of heel pain

Lifetime prevalence 10%

Pathophysiology

Chronic degeneration resulting from repetitive stretching and tearing, rather than from in ammation

Anatomy

Triangular thickened brous aponeurosis

Five digital bands providing investing sheaths for plantar exor tendons and small plantar nerves

Shock absorber

Provides tension and support to the arch of the foot

Innervation of heel skin

The medial calcaneal nerve, a branch of the tibial nerve, can be involved proximally in tarsal tunnel syndrome

First branch of the lateral plantar nerve (Boxter's nerve), distal to medial of the calcaneal tuberosity. This nerve is at risk of entrapment between the adductor hallucis muscle and the medial belly of the quadratus plantae muscle

Risk factors

Chronic axial overload:

Physical exercise, e.g. long-distance running, ballet

Obesity

Occupational—teachers, factory workers, policemen

Anatomical— at feet, high-arched feet, shortened Achilles tendon

Biomechanical—overinversion, limited ankle dorsi exion, weak plantar exors, weak intrinsic muscles of the foot

Environmental—deconditioning, walking barefoot or on hard surfaces, poor footwear

Symptoms and signs

Common in those aged 40–60, who are on their feet for extended periods of time

Under-surface of the heel is very painful on weight-bearing, worse after a period of immobility

Gradual onset of pain on the medial side of the heel, intense in the morning and radiating to the arch of the foot

Tenderness over the medial calcaneum

Windlass test: pain reproduced on passive dorsi exion of the toes

Investigations

Imaging—not necessarily useful:

- USS—swelling of plantar fascia
- X-ray—calcaneal spur

Di erential diagnosis

Achilles tendinitis:

- Tenderness over posterior aspect of the heal and along Achilles tendon
- Pain radiates up to calf muscles
- Pain can be reproduced by foot extension or standing on tiptoes

Calcaneal stress fracture:

- Presents with di use, warm swelling, characterized by resting pain and reproduced by squeezing the calcaneum

Subcalcaneal bursitis:

- Posterior heel pain under the calcaneal fat pad
- Not reproduced by foot or toe dorsi exion

Tarsal tunnel syndrome:

- Poorly localized pain
- Numbness and burning on medial foot and ankle and sometimes over calf muscles
- Reproduced by Tinel's test: tapping with ngers or tendon hammer posterior to the medial malleolus

Management

Early plantar fasciitis—conservative treatment; majority will completely recover within 6 months; heat, cold

Patient education and intensive rehabilitation

Correct reversible causes

Insoles and heel pads to correct foot pronation

Physical therapies:

- Stretching of plantar fascia—towel looped around foot which is pulled with extended knees, causing active dorsi exion
- Calf stretches with slightly exed soleus and fully extended knee
- Night splints or Strasbourg socks, hold foot in dorsi exion, facilitating passive plantar fascia stretch
- Massage with golf ball beneath painful arch

Pharmacological management, as per NICE recommendations:

- Paracetamol ± codeine
- NSAIDs

Interventional management:

- Steroid injection, preferably US-guided, from the side of the fascia as there is a risk of rupture of the plantar fascia in 10% of cases if direct injection into the plantar fascia
- RF ablation of the sensory branch of the medial calcaneal nerve and the first branch of the lateral plantar nerve
- Localized injection of autologous PRP—promising early result; however, lack of long-term evidence
- Plantar fascia release surgery may be tried when conservative management has been tried for 6–12 months without success
- Extracorporeal shockwave therapy (ECSWT): NICE-approved for intractable plantar fasciitis

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CHAPTER 24

Neuropathic Pain Conditions

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24.1 Post-stroke pain

De nition

Pain caused by a primary lesion or dysfunction in CNS or peripheral nervous system associated with abnormal sensitivity to temperature and noxious stimulation

Arises within weeks to months after stroke

Associated with the presence of depression, cognitive dysfunction, and impaired QoL

Chronic pain syndromes are present in up to half of the patients

Types and incidence

Post-stroke pain—30–40% initially, decreasing to 20% after 1 year

MSK pain (including shoulder pain and subluxation)—70%

Central post-stroke pain—8–30%

CRPS type 1—10–30%

Painful spasticity

Pathophysiology

Interplay between peripheral nociceptive pain generators and central neuropathic generators, in concert with altered CNS pain signal processing and neuromodulation

Any lesion of the CNS can be implicated

Central post-stroke pain occurs due to a lesion in the spino-thalamo-cortical pathway and arises more often from non-thalamic than from thalamic lesions. Common after lateral medullary infarct or lesions in the ventro-posterior thalamus

Central and peripheral sensitization plays a signi cant role

No patterns of symptoms pertaining to any particular lesion

Can occur after haemorrhagic or ischaemic cerebral events

Loss of a erent input causes neuronal hyperpolarization. Hyperpolarization of neurons with disinhibition of the CNS descending pathway

Clinical features

Nociceptive pain is associated with tissue damage and is mediated by an intact nervous system

Neuropathic pain is caused by injury to, or dysfunction of, the peripheral and/or central nervous system

Central post-stroke pain—spontaneous and continuous pain and sensory changes in the area corresponding to the stroke lesion; may present as burning, lancinating pain, with allodynia and hyperpathia

Management

Central post-stroke pain—challenging to treat, with mixed results; principles include reducing peripheral and central sensitization, decreasing DRG activity, and increasing central inhibition

- Pharmacological—trial of antidepressants, anticonvulsants, antiarrhythmic drugs (mexiletine), ketamine, cannabinoids, topical lidocaine/capsaicin, opioids. Evidence suggests cannabinoids and TCAs > pregabalin/lamotrigine
- Neurostimulation—TENS, cervical spinal cord stimulator, epidural motor cortex stimulation (MCS), thalamic DBS, motor cortex repetitive transcranial magnetic stimulation (rTMS)

Spasticity—baclofen, local neuromuscular blockade (botulinum toxin). LA blocks may provide short-term relief of pain and spasm, and allow active and passive movement of the joints

Pain related to posture and immobility—speci c mobilization procedures, alterations to nursing

Shoulder pain—could result from glenohumeral subluxation, and strategies designed to improve the ROM and function of the glenohumeral joint (surface electrical stimulation, passive mobilization) should be used

Rehabilitation: experienced physiotherapists teaching desensitization techniques, biofeedback, relaxation, family education, and involvement in rehabilitation

Other/additional information

Dejerine–Roussy syndrome is the best-characterized central post-stroke pain syndrome. This thalamic pain syndrome is due to infarction of the ventroposterolateral thalamus, accounts for approximately one-third of the cases of central post-stroke pain, and is characterized by severe and paroxysmal pain, accompanied by allodynia and hyperalgesia

Further reading

1. Boivie J. Central pain. In: Wall P, Melzack R (eds). Textbook of Pain. 4th edition, 1999; pp. 879–914. London: Churchill Livingstone
2. Klit H, Finnerup NB, Jensen TS. Central post-stroke pain: clinical characteristics pathophysiology, and management. Lancet Neurol 2009; 8: pp. 857–68.

24.2 Chronic in ammatory demyelinating polyneuropathy

Introduction

Immune-mediated disorder of the peripheral nervous system

Rare condition—30% of patients are cured or in long-term remission, and 18% have unstable active disease (progressive/relapsing) which may lead to substantial disability

The pathogenesis is incompletely understood and includes several humoral and cell-mediated mechanisms

Similar to Guillain–Barré syndrome but produces chronic weakness, which is either progressive or relapsing and remitting

Clinical features

Most patients have a slowly progressive symmetrical polyneuropathy

In some patients, the course can be relapsing or progressive for >2 months

Prominent proximal and distal muscle weakness

Sensory loss in distal limbs—loss of vibration sense and joint position is more pronounced than loss of pain and temperature sensation

Poor balance, pain, and impaired ambulation

Generalized hypore exia or are exia

Di erent presentations of this condition:

- Sensory-predominant: dysfunction of large sensory bres
- Distal and sensory demyelinating symmetric neuropathy
- Proximal variant a ecting the dorsal sensory nerve roots (large- bre sensory dysfunction). Presents with symmetrical sensory ataxia and decreased vibration and proprioception
- Lewis–Sumner syndrome: asymmetrical, multifocal sensory and motor neuropathy

Investigations

Lumbar puncture: raised protein without pleocytosis in the CSF

MRI: gadolinium enhancement and/or hypertrophy of brachial or lumbo-sacral plexuses, lumbo-sacral or cervical nerve roots, or cauda equina

NCS: evidence of demyelinating neuropathy

Nerve biopsy: segmental demyelination (without or with in ammation)

Treatments

Disease-speci c treatments—immune-modulating therapy

First line: corticosteroids, plasma exchange, or IV immunoglobulin (Ig) on their own or used in combination in severe cases

Second line: azathioprine, methotrexate, ciclosporin, cyclophosphamide, tacrolimus, mycophenolate, etanercept

Other: stem cell transplant

Multidisciplinary treatments

Multimodal addressing biological (disease-speci c, surgical, analgesic), physical, psychological (psychiatric or psychological), and social (work, litigation, social support network) contributors to pain, disability, and distress

Regular exercise, nutrition, and healthy lifestyle

Additional information

Accurate diagnosis can be improved using the European Federation of Neurological Societies and Peripheral Nerve Society diagnostic criteria

Other neuropathies can have a similar presentation:

- Infections: diphtheria, *Borrelia burgdorferi* infection (Lyme disease), drugs, or toxins
- Hereditary demyelinating neuropathy
- Multifocal motor neuropathy
- IgM monoclonal gammopathy
- Other demyelinating neuropathies: osteosclerotic myeloma, diabetic and non-diabetic lumbo-sacral radiculopathic neuropathy, peripheral nervous system lymphoma, amyloidosis

Further reading

1. Lewis AR, Shefner JM, Dashne JF. Chronic in ammatory demyelinating polyneuropathy. 2020. https://www.uptodate.com

24.3 Multiple sclerosis

De nition

An immune-mediated disorder of the CNS characterized by demyelination at multiple times over multiple sites

Incidence

In 2010, the prevalence was 285.8 and 113.1 per 100 000 women and men, respectively

Peak incidence occurs between the ages of 40 and 50

Female:male ratio—close to 3:1

A total of 203 people per 100 000 were living with MS, and 6003 new cases were diagnosed in that years

Pathophysiology

MS involves a two-stage degenerative process

Acute phase (in ammatory stage)—in ammatory cells enter the CNS and, via several mechanisms, damage endothelial cells, while also attracting macrophages which create further demyelination

Chronic phase—involves ongoing loss of axonal support, causing chronic degeneration. Loss of oligodendrocytes, astrogliosis, and demyelination occur. Loss of myelin sheath is responsible for cross-excitation and can eventually cause peripheral and central (dea erentation) neuropathic pain

Aetiology/risk factors

Genetic factors play a signi cant role, with rst-degree relatives having a 20- to 40-fold increased risk

Geographic factors also contribute, with incidence increasing away from the equator to the poles

Diagnosis

The McDonald criteria (revised in 2010) provide a framework on which a diagnosis of MS can be made; it stipulates a combination of clinical and radiological (MRI) ndings to demonstrate damage to the CNS in both space and time (see Table 24.3.1)

Clinical presentations can include: loss or reduction of, or double, vision; ascending sensory or motor symptoms; cerebellar disturbance; or Lhermitte's syndrome (sensory changes on neck exion)

Exclusion of any other diagnosis

The di erential diagnosis can be extensive and can be approached by looking for suggestions that another presentation is more likely. These may be rare symptoms in the presentation of MS, such as peripheral neuropathy or hearing loss, or patient factors such as age (presentation before the age of 20 or after 50) or a strong family history of other diseases

Treatment

Education

Lifestyle advice, such as stopping smoking and taking exercise, helps reduce relapse rates

Physical and psychological therapy

Can help with fatigue, spasticity, and mobility issues, as well as with mood disturbances

Pharmacological management

Management of relapses—con rm relapse by ruling out infection and disease uctuation. The mainstay of treatment of a relapse is methylprednisolone 0.5 g/day for 5 days

Disease-modifying therapy (DMT), e.g. alemtuzumab, -interferon and glatiramer acetate, cladribine

Symptomatic treatment for pain, incontinence, mobility, fatigue, memory, and spasticity

Table 24.3.1 McDonald criteria for MS

Number of clinical attacks	Objective evidence of lesions on MRI	Additional criteria
2	2	None needed
2	1	DIS (or wait for another clinical attack at another site)
1	2	DIT (or wait for another clinical attack at another site)
1	1	DIS and DIT (or wait for another clinical attack at another site)
0		Disease progression in 1 year and at least two or three points mentioned below: 1. DIS in brain 2. DIS in spinal cord 3. CSF positive

DIS, dissemination in space; DIT, dissemination in time.

Adapted with permission from McDonald W., Compston, A., Edan, G. et al. (2001). Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol.* 50(1):121-7. doi:10.1002/ana.1032

Neuropathic pain is best treated using NICE neuropathic pain guidance, while baclofen can be used for spasticity and amantadine for fatigue

Botulinum toxin and IT baclofen have both been used in people with resistant spasticity. Sativex® (THC:CBD spray) is no longer recommended for treatment of spasticity in MS patients

Other/additional information

NICE recommends that all patients with MS have an annual comprehensive review covering all aspects of their care by people expert in the eld

Further reading

1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol 2011;69(2):292–302
2. National Institute for Health and Care Excellence. Multiple sclerosis in adults: management. 2014; updated 2019. https://www.nice.org.uk/guidance/cg186

24.4 Spinal cord injury

Introduction

Trauma is the most common cause of SCI. More common in males

Incidence in the UK is 12–16 per million of the population

Chronic pain is common (70%) and normally associated with signi cant impact on mood, functioning, QoL, and productivity

Most common types of pain are nociceptive (MSK or visceral) and neuropathic

Pathophysiology

Nociceptive pain from activation of MSK and/or visceral nociceptors

Neuropathic pain:

- Peripheral pain generators from the peripheral somato-sensory nervous system can be involved
- Spinal cord mechanisms:
  - Hyperexcitable neurons
  - Autonomic, in ammatory, and immunological changes (e.g. glial activation)
  - Structural neuroplasticity (e.g. dendritic sprouting)
  - Functional changes in ion channels (e.g. Na^+ and Ca^{2+}) and receptors (e.g. NMDA)
  - Spinal cord dea erentation (partial or complete) leads to white matter loss and hypersensitivity in the spinal cord
- Supra-spinal mechanisms (may develop as a consequence of the SCI):

Cortical reorganization (functional and structural)

Changes in anterior cingulate cortex and prefrontal cortex

Changes in thalamus (abnormal bursting, thalamo-cortical dysrhythmia)

Below-level neuropathic pain is mostly centrally mediated (neuronal hyperexcitability), but the mechanism is not clear. The mechanism of evoked and spontaneous pain is di erent in complete and incomplete injuries. Functioning peripheral nerve bres (polysynaptic, A-delta, C- bres, or other) in incomplete SCI patients transmit peripheral

thresholds to the spinal cord from the injury site and periphery. Some patients have subclinical preservation of some spinal cord pathways on neurophysiological testing (QST) despite having a 'complete' SCI

Clinical features

Neuropathic pain

SCI commonly presents with several types of neuropathic pain outlined in the IASP taxonomy of pain after an SCI. Criteria for SCI-related neuropathic pain include:

- History and diagnostic test con rming SCI
- Pain distribution is at or below the neurological level
- Negative or positive sensory symptoms and clinical signs of neuropathic pain
- Other causes of pain excluded or unlikely

Neuropathic pain is common and classi ed as follows:

- Above-level neuropathic pain originates from pathologies above the level of the SCI such as CRPS or peripheral nerve injury
- At-level neuropathic pain arises from the spinal cord and/or nerve roots. Presents in two dermatomes above or below the level of the injury
- Below-level neuropathic pain is localized below the level of the injury
- Other causes of neuropathic pain such as diabetic neuropathy, PHN or other causes

Musculoskeletal pain

Acute MSK pain from in amed or damaged MSK structures (tendons, muscles, bones, ligaments, joints)

Chronic MSK pain commonly caused by MSK overuse or strain. Chronic wheelchair use can cause carpal tunnel syndrome, nerve entrapments, and thoracic outlet syndrome. Back and neck MSK pain is common, especially in patients with paraplegia and spinal fusion surgery. Pain from muscle spasms is also common

Visceral pain

From nociceptors located in the pelvis, abdomen, or thorax. Some examples include constipation, peptic ulcer, appendicitis, cholecystitis, and MI

Other causes of pain

Nociceptive causes such as surgical scar incision, autonomic dysre exia headache, etc.

Other causes of pain such as bromyalgia, interstitial cystitis, etc.

Sometimes the cause of the pain is unknown

Assessment

Pain-orientated detailed history, questionnaires, system based examination (neurological and musculoskeletal systems are normally very important)

Important to assess psychosocial factors and associated pain-related disabilities

Neurological examination to determine the sensory and motor level, whether injury is complete or incomplete (incomplete injuries have sensory and/or motor function in S4–5), and score on the American Spinal Injury Association Impairment scale

Investigations:

- Blood tests such as folate, metabolic pro le, vitamin B12, and vitamin D which can contribute to neuronal dysfunction

X-ray, CT, and MRI if suspected spinal segmental instability, compression, peripheral nerve compression, syringomyelia, hardware instability, or structural pathology

Endoscopy, barium studies, cystoscopy, and urodynamic studies may be indicated for visceral pain in the pelvis, abdomen, or thorax

NCS for neuropathies

Bone scans for in ammatory processes in bone such as infections, fractures, and CRPS

QST and contact pain-evoked potentials not available in clinical practice routinely

Treatment

Whenever possible, treat the underlying pathology. Most treatments for pain management are aimed at providing symptomatic relief and have limited evidence of e cacy

Gold standard is multidisciplinary treatments with input from a psychologist, physiotherapist, OT, nursing, pharmacy, dietician, and doctor, targeting function, productivity, rest, leisure, vocation, relationships, motivation, and mood

CBT improves pain behaviour, mood, and coping mechanisms

OT and physiotherapy improve overuse syndrome, tness, abnormal postures, and gait. Treatments can include education, exercise, hydrotherapy, training with day-to-day activities (transferring, using the wheelchair, changing lifestyle), and environmental modi cations

Pharmacological treatments:

- Long-term use of analgesics should be minimized due to associated S/Es and adverse e ects (particularly opioids and benzodiazepines)
- MSK pain: paracetamol, NSAIDs, and opioids as per WHO ladder. Baclofen, botulinum toxin, and BZDs can be considered for pain from muscle spasms
- Neuropathic pain can be treated with antidepressants (amitriptyline, duloxetine, dosulepin), anticonvulsants (pregabalin, gabapentin), and opioids (e.g, tramadol, tapentadol) ketamine and lidocaine can be e ective in acute neuropathic pain
- Severe vasomotor changes with regional pain: sympathomimetics, Ca^{2+} channel blockers, interventional blocks
- Regional trophic changes and osteopenia: bisphosphonates, calcitonin
- Depression, insomnia, anxiety: antidepressants that have analgesic properties ideally, anxiolytics, psychotherapy

Surgery may be required to reverse structural problems that are contributing to pain (e.g. surgical decompression for peripheral nerve compression, drainage of syringomyelia, dorsal root entry zone lesioning)

Neuromodulation can be considered for refractory pain:

- IT pumps can be used to treat neuropathic pain or muscle spasticity. Combination therapies are successful, involving baclofen, clonidine, morphine, and ziconotide
- SCS e cacy is controversial probably due to impaired DH function. Patients with incomplete injuries get more pain relief with SCS than the complete lesion
- Other neurostimulation techniques that can be considered include TENS, transcranial magnetic stimulation, PNS, and MCS

Further reading

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4. Siddall PJ, Yezierski RP, Loeser JD. Taxonomy and epidemiology of spinal cord injury pain. In: Burchiel KJ, Yezierski RP (eds). Spinal Cord Injury Pain: Assessment, Mechanisms, Management. Progress in Pain Research and Management. 2002; pp. 9–24. Seattle, WA: IASP Press

24.5 Cauda equina syndrome

Introduction

Presents commonly with acute-onset urinary retention or incontinence or faecal incontinence accompanied by altered perineal sensation secondary to a large central lumbar disc prolapse compressing the cauda equina nerves in the spinal canal

Incidence

4/10 000 adults with back pain

1–2% of surgically treated lumbar disc prolapses

Can be either sudden onset without previous problems or can occur in patients with chronic non-cancer low back pain radiating down the leg

Anatomy

Sacral nerve roots pass centrally in the theca in the spinal canal. S2–4 supply sphincter function. Central lumbar spinal canal compression can compromise innervation of the sphincters and perineum

Pathophysiology

Rupture of the annulus brosus, causing the nucleus pulposus to herniate posteriorly

More common in young adults <60 years old as discs degenerate and desiccate with age

More common in obese patients due to greater axial loading of the spine and relatively weaker paraspinal musculature limiting load distribution

Diagnosis

Diagnosis is mostly made from the history

Loss of sensation of micturition or defecation

Acute-onset urinary dysfunction, progressing to painless urinary retention and over ow incontinence

Faecal incontinence

Perineal paraesthesiae/anaesthesia

Sexual dysfunction (impotence)

Leg pain and weakness (often bilateral)

Examination and investigations

Saddle anaesthesia

Reduced or absent anal tone in two-thirds of patients

Reduced or absent anal wink re ex

Reduced or absent bulbocavernosus re ex

Absent ankle jerk re exes

MRI scan of the lumbo-sacral spine is mandatory to make diagnosis

Aetiology

Usually massive herniated lumbar disc

Sometimes tumour (metastatic spinal cord compression or intradural lesion)

Occasionally trauma (burst fracture with retropulsed fragment)

Seldom spondylodiscitis

Rarely spinal epidural haematoma or abscess

Non-surgical causes include septic thrombophlebitis, ischaemia, in ammation, and paraneoplastic or metastatic tumour seeding

Treatment

Surgical emergency: urgent decompression by discectomy within 48 hours of symptom onset provides the best chance of recovery of sphincter function

Generous bilateral laminectomy before discectomy is often preferred to a limited microdiscectomy approach. Occasionally, an intradural approach is needed

If >1-week history of double incontinence, then expedient surgery desirable, but less urgent as sphincters usually irreversibly impaired

Post-operative bladder function assessment by catheter clamping before removal; post-voiding residual measurement is important and prompt urology referral should be made for residual sphincter impairment

Recovery of sensory and motor function may continue for up to 2 years. Recurrent disc prolapse is a small, but important, risk

Medical management: steroids and radiotherapy

Further reading

1. Gleave JR, Macfarlane R. Cauda equina syndrome: what is the relationship between timing of surgery and outcome? Br J Neurosurg 2002;16(4):325–8
2. Todd NV. Neurological deterioration in cauda equina syndrome is probably progressive and continuous. Implications for clinical management. Br J Neurosurg 2015;29(5):630–4

24.6 Trigeminal neuralgia

Introduction

Trigeminal neuralgia is:

A rare condition, characterized by recurrent paroxysmal, unilateral, brief electric shock-like pains, abrupt in onset and termination

Limited to the distribution of one or more divisions of the trigeminal nerve

Triggered by innocuous stimuli

Idiopathic or secondary to other disorders

Persistent background facial pain may be present

Epidemiology

Incidence of approximately 12/100 000 people/year

More common in women

Commonly in people over the age of 50 but can occur at any age

MS may be a possible secondary cause in young adults

Anatomy

(See 16.2 Anatomy of the trigeminal nerve and trigeminal ganglion block, p. 301.)

The trigeminal nerve exits the brainstem laterally at the mid-pons level and has two roots—a larger sensory root and a smaller motor root

The motor root also contains sensory nerve fibres that mainly mediate pain sensation

The Gasserian ganglion, located in Meckel's cave in the middle cranial fossa, is the ganglion of the trigeminal nerve and contains first-order general somatic sensory fibres that carry pain, temperature, and touch sensation

The peripheral processes of neurons in the ganglion form the three divisions—ophthalmic, maxillary, and mandibular

The sensory trigeminal nerve nuclei are the largest of the cranial nerve nuclei and extend from the midbrain to the high cervical cord

Pathophysiology

Vascular compression from either an artery or a vein of the trigeminal nerve root occurs, with morphological changes in the nerve in about 95% of patients

The exact pathophysiology of compression causing pain is unknown

A combination of central demyelination of the nerve root entry zone and reinforcing electrical excitability may be a hypothesis. This demyelination leads to impairment of the nociceptive system

In patients with more background facial pain, there seems to be loss of central inhibition of the nociceptive system, which persists even after successful surgery, manifesting as some form of abnormality of somato-sensory function

There are also trigeminal neuralgia cases associated with MS plaques or infarcts within the brainstem or cerebellopontine mass lesions

Diagnosis

Classical trigeminal neuralgia

Pain usually occurs in the V2 or V3 distributions

Evidence of neurovascular compression of the trigeminal root with morphological changes on MRI or during surgery

The hallmarks include memorable onset, initial long remission periods that become shorter with time, and longer attacks of pain

65% of newly diagnosed patients with classical trigeminal neuralgia have a second episode within 5 years, and 77% within 10 years

50% may have remission periods of at least 6 months' duration

Attack frequency can vary throughout the day

Two subcategories exist: classical trigeminal neuralgia, purely paroxysmal, and classical trigeminal neuralgia with concomitant persistent facial pain (atypical trigeminal neuralgia)

Autonomic features are rare

Diagnostic criteria for the two forms of classical trigeminal neuralgia (see table 24.6.1)

Table 24.6.1 Diagnostic criteria for the two forms of classical trigeminal neuralgia

	Classical trigeminal neuralgia, purely paroxysmal	Classical trigeminal neuralgia with concomitant persistent facial pain
Features	Recurrent paroxysmal attacks lasting seconds to minutes Severe intensity Electric shock-like shooting, stabbing or sharp in quality Precipitated by innocuous stimuli to a ected side of the face Occurs in one or more divisions of the trigeminal nerve No radiation beyond the trigeminal distribution No clinically evident neurological de cit	
Facial pain	No persistent facial pain between attacks	Persistent facial pain of moderate intensity in the a ected area
Response to treatment	Responds well initially to medical treatment; good response to microvascular decompression	Responds poorly to conservative treatment and surgical intervention
Other features	Never crosses to opposite side, rarely may be bilateral	

Source: Data from *The International Classi cation of Headache Disorders*, Third Edition. London, United Kingdom: International Headache Society.

Secondary trigeminal neuralgia

Other causes of pain include MS plaques, tumours in the cerebellopontine angle, and arterio-venous malformation

Patients with MS present at a much younger age, with atypical pain, without the trigger zones and the lancinating brief paroxysmal period. It can be bilateral and can be challenging to manage

Imaging is mandatory for diagnosis

Treatment

Medical treatment

First-line treatment of trigeminal neuralgia

Carbamazepine is the drug of choice, which provides excellent initial pain relief in the majority of patients. It should be started at a low dose and gradually increased every 3–7 days to achieve best pain control with minimal S/Es

Common S/Es include tiredness and poor concentration. At higher doses, balance impairment and hyponatraemia are common, especially in the elderly. Occurrence of a rash requires discontinuation of the drug

The second drug of choice is oxcarbazepine, a keto derivative of carbamazepine, with similar e cacy, but with increased tolerability and fewer drug interactions

If patients are intolerant of the above drugs, then lamotrigine, baclofen, pregabalin, or phenytoin can be tried

Patients should be referred onwards to a specialist in managing trigeminal neuralgia, as S/Es with combination therapy are high and best managed in a specialized setting

Surgical treatment

Indicated for patients in whom medical treatment has failed or S/Es associated with medical treatment are unacceptable

Surgical options fall into two categories: microvascular decompression or destructive procedures

Microvascular decompression

Has the highest success rate in maintaining long-term pain relief

O ers an 80% chance of being pain-free without the need for any further treatment, with a recurrence rate of about 10% over 20 years

It consists of a small craniotomy in the mastoid region, gently separating the nerve from the o ending blood vessel and holding it in place with a small piece of Te on. In cases where vascular compression is not evident, a partial neurectomy of the nerve near the root entry zone may be performed. A neurectomy causes numbness in the face, with the risk of causing anaesthesia dolorosa

Risks of surgery include hearing loss, damage to the trigeminal nerve causing permanent facial numbness, CSF leak, and meningitis

Destructive procedures

These procedures involve partial controlled damage to the trigeminal nerve root with the aim to relieve pain. It can be used for all causes of trigeminal neuralgia and is performed with either sedation or light general anaesthesia, ideal in the elderly or medically un t patients. Some options include:

Balloon compression: a soft catheter with a balloon is inserted into the foramen ovale through the cheek under radiological guidance and in ated to compress the nerve. Pain relief usually lasts 1–2 years and can be repeated. A common S/E is numbness of the face, including that of the cornea

Glycerol injection: glycerol is injected via a needle inserted through the cheek into the foramen ovale, with the patient in the sitting position (glycerol is heavier than spinal uid). The glycerol bathes the ganglion and damages the nerve bres. Recurrence within a year or two is frequent and the procedure can be repeated. Facial sensation loss is a common S/E

RF ablation: via a needle inserted into the foramen ovale to target the area of pain, the nerve area is gradually heated with an electrode, injuring the nerve bres. Symptoms recur in 50% of patients 3–4 years following lesioning. Production of more numbness can extend the pain relief even longer but increases the risks of anaesthesia dolorosa

Stereotactic radiosurgery: highly focused radiation beams are delivered to the nerve root exit zone at the brainstem. Radiation causes the formation of a lesion on the nerve that disrupts sensory signal transmission to the brain. Pain relief is usually evident weeks to months later and appears to be as e ective as with other percutaneous procedures. Recurrence rates are around 25% between 1 and 3 years

Emergency treatment

Severe acute pain can stop the patient eating and drinking and can lead to severe dehydration and possible hyponatraemia caused by oral medications

Opioids use has no e ect

Admission to hospital for pain management, correction of biochemical abnormalities, and IV hydration is required

In many cases, a single dose of IV phenytoin with cardiac monitoring helps to break the pain cycle and can be instituted together with an increase in oral medications

Good oral hygiene required to prevent any additional dental pain

Percutaneous procedures (e.g. balloon compression) can be utilized to manage the acute pain

Stereotactic radiosurgery is not recommended as an emergency treatment, given the lag time before results are noted

Further reading

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24.7 Glossopharyngeal neuralgia

Introduction

Glossopharyngeal neuralgia presents with pain in the sensory distribution of CN IX

First described by Weissenberg in 1910 in a patient with a cerebellopontine angle tumour

Clinically resembles trigeminal neuralgia but occurs 100 times less often

Incidence rate is 0.7 cases per 10 000 population

Clinical features

Usually a ects patients in the fth decade of life but may occur at any age

Patients present with otalgia (most common), tonsillar pain, laryngeal pain, and glossal pain—in that order

Paroxysmal pain lasting seconds to minutes

Common triggers are swallowing, chewing, talking, and coughing

'Over ow pain'—20% of patients have pain in the sensory areas supplied by CN V, CN X, and upper cervical segments. This is due to spillover of nociceptive impulses from CN IX through the nucleus tractus solitarius of the medulla to CN V or convergence with the descending portion of CN V

Several hypotheses describe a synapse between CN IX and CN X that results in pain associated with bradycardia and syncope

Investigations

Baseline blood tests and MRI to rule out a cerebellopontine angle tumour and demyelinating diseases

Management

Multidisciplinary and multimodal treatments

Pharmacotherapy:

- First line: carbamazepine
  - Start with 200 mg nocte, and increase in 200 mg increments up to a maximum dose of 1200 mg daily
  - Common S/Es: dizziness, sedation, confusion, and rash

Monitor FBC, serum chemistry, and urinalysis

Monitor actively for life-threatening blood dyscrasias

Second line: oxcarbazepine, gabapentinoids, antidepressants, baclofen

Glossopharyngeal nerve block:

Transoral, transnasal, and lateral infratemporal approaches

Potential complications: haematoma formation (injury to internal jugular vein or carotid artery), CSF leak, LA toxicity

A successful diagnostic block may be followed by RF procedures

Neuro-destruction with phenol, alcohol, and glycerol is reserved for selective patients in whom drug therapy has failed

Microvascular decompression (Jannetta technique): a neurosurgical procedure that identifies the nerve root close to the brainstem and decompresses the offending blood vessel, with positioning of the sponge in between the vessel and the glossopharyngeal nerve

Further reading

1. Bajwa Z, Ho CC, Khan SA, Garza I. Overview of craniofacial pain. 2018. https://www.uptodate.com

24.8 Occipital neuralgia

Definition

Stabbing and shooting paroxysmal pain, along the dermatome of the GON (90%) and LON (10%)

Damage and/or irritation of the nerves causes neuralgia

Pain elicited by pressure over the nerves, along the nuchal ridge or on rotation and lateral flexion of cervical spine, with constant pain in between episodes

Course of the nerve

The GON is formed by the dorsal ramus of C2, has a medial course under the IO muscle, bending cranially, and finally turns laterally, piercing the semispinalis muscle and the aponeurosis of the trapezius muscle, after which it divides and lies SC

Causes

Vascular—irritation of C1/C2 nerve roots by aberrant branch of the posterior inferior cerebellar artery, giant cell arteritis, arterio-venous fistula at the cervical dural level

Neurogenic—MS, C2 myelitis, schwannoma of the occipital nerve

Muscular/tendon involvement

Bone—C1/C2 arthritis, dysfunction of the atlas bone, osteolytic lesions of the cranium

Post-vitrectomy surgery

Clinical features

Pain in the neck radiating to the posterior cranium to the top of the head, over the ear, and parotid gland

Attacks lasts for seconds to minutes

Sharp pain and electric shock-like sensation, and may be triggered by brushing hair, neck movements, or resting the head on a pillow

Pain may be referred in the retro-orbital and frontal head regions, and felt usually unilaterally and occasionally bilaterally

Examination

Sensory changes and tenderness in the dermatome

Positive Tinel's sign—pain on percussion of the nerve

Investigations

Baseline blood tests, CT, and MRI are needed to rule out tumours, cervicalgia, and other causes of secondary headaches

Open-mouth X-ray—arthritis of the C2 facet joint

Diagnostic blocks of GON and LON are helpful

Di erential diagnosis

Tension-type headache, migraine, cervicogenic headache

Occult tumour, congenital anomalies (Arnold–Chiari malformation)

Cervical disc disease, OA

Gout, diabetes

Infection, vasculitis

Treatment

Conservative

Physical therapy, massage, improving posture, and reducing secondary muscle tension

Pharmacological therapy:

- Anti-in ammatories
- Antidepressants (especially TCAs)
- Antiepileptics (gabapentinoids, carbamazepine)
- Muscle relaxants (baclofen, tizanidine)

Interventions

Occipital nerve blocks (GON and LON, and occasionally TON) with LA and steroid mixtures

BTX-A injection

PRF of the occipital nerve may help

PRF of the C2 DRG—very limited evidence

PENS and ONS can be helpful. Electrical impulses are delivered via insulated lead wires tunnelled under the skin. It is relatively minimally invasive and can o er long-term bene t

Microvascular decompression of C2 nerve root, DRG, or post-ganglionic nerve is practised in some specialist centres

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24.9 Post-herpetic neuralgia

De nition/introduction

Post-herpetic neuralgia (PHN) is neuropathic pain in a dermatome due to damage to a peripheral nerve during an outbreak of shingles (pain that continues for >3 months)

PHN is the most common complication of shingles (sensory nerve bres and skin are a ected; motor bres are rarely a ected)

Chickenpox (varicella) is caused by initial infection with the varicella zoster virus (VZV) (skin rash, small itchy blisters ± fever, tiredness, headaches)

VZV is one of the herpesviruses

Shingles (herpes zoster) are caused by reactivation of the herpes zoster virus (approximately 20% lifetime prevalence)

Incidence

For herpes zoster: 0.34%, but almost tripled in the elderly population above the age of 80

Even higher in individuals with low cell-mediated immunity

Incidence in the elderly will become even higher with universal immunization of children with varicella, as the boosting e ect on cell-mediated immunity due to exposure to varicella will be lost

For PHN: 10–18% of patients with herpes zoster (under 60 <10%, over 60 up to 30–40%)

Pathophysiology/anatomy

After initial infection (chickenpox, varicella), the VZV remains dormant in the DRG

All individuals once infected with varicella undergo seroconversion. They remain at risk of developing shingles and its complications, including PHN

VZV is reactivated whenever there is a decline in immunity, causing shingles

During reactivation, the VZV travels down the axons from DRGs to the skin in the periphery to cause a rash or blisters

VZV can also end up travelling centrally to a ect the meninges and spinal cord, resulting in their in ammation

The course of the disease is usually mild, with pain in most cases subsiding, with scabbing of the rash or even before that

Shingles can also result in other complications, including visceral, neurological, and ophthalmic disorders

Mostly a ected areas: thoracic dermatomes, ophthalmic division of the trigeminal nerve (ophthalmic shingles)

Risk factors to develop post-herpetic neuralgia after shingles

Age: older than 50

Severity of shingles: extensive/severe rash and severe pain and associated sensory abnormality in the early phase

Other illness: chronic disease (diabetes), immunosuppression

Shingles location: on the face or torso

Delay in shingles antiviral treatment for >72 hours after the rash appeared

Diagnosis

Mainly clinical diagnosis, with signs and symptoms limited to the skin area where the shingles outbreak first occurred (usually unilateral in a band around the trunk)

Pain lasting >3 months after the shingles rash has healed; presentation of burning, sharp, and stabbing or deep and aching pain (usually T4–6 dermatomes but can also affect cervical and trigeminal nerves)

Frequently with allodynia (even touching clothes can cause pain)

Less commonly with itching and areas of numbness/reduced sensation

Although it presents as a continuum of pain after the rash, it can also present years after the initial rash; in these patients, polymerase chain reaction (PCR) test detecting VZV in the CSF may help the diagnosis

Antibodies to herpes zoster (4-fold increase) to support subclinical herpes zoster

Viral culture or immunofluorescence to differentiate between herpes simplex and herpes zoster

Possible complications

Depending on the duration of PHN and the severity of pain, patients can develop depression, fatigue, difficulty sleeping, lack of appetite, and concentration problems

Treatment

Biopsychosocial approach

Pain can persist for years and can be difficult to treat

Pharmacological options (tricyclic antidepressants, anticonvulsants, topical agents, opioids)

Tricyclic antidepressants

These are found to be effective for PHN treatment as their action is multimodal, i.e. by potentiation of the effects of neurotransmitters in the descending pain modulatory pathways, blockade of Na^+ channels, and blockade of -adrenoceptors

Amitriptyline, nortriptyline (NNT = 3.7)

Anticonvulsants

Gabapentin and pregabalin are effective

Pregabalin with superior bioavailability and less associated adverse effects. Also improved stage 4 sleep, resulting in improved QoL in patients

Topical agents

Lidocaine patch:

- Several studies and systemic reviews support the use of lidocaine patches (5%) in the treatment of PHN (NNT = 4.4 for pain)

Topical capsaicin:

- Vanilloid receptor agonist with multiple modes of action, including inactivation of receptive terminal of nociceptors, depletion of SP, and as a C- fibre nerve toxin
- Effective in low concentration of 0.025% or 0.075% (cream), applied 4–5 times per day, as well as in high concentration of 8% (patch), applied for 30–60 minutes (higher concentration more effective in a double-blind RCT)

Opioids (e.g. codeine, tramadol, morphine)

Opioids can be quite e ective for PHN, with morphine having an NNT value of 2.79 against an NNT of 3.73 for nortriptyline in a double-blind crossover study

Considered as second or third choice due to S/Es and tolerance, and dependence with prolonged use

Non-pharmacological options

Wear comfortable clothes, ice packs

TENS or acupuncture (lack of evidence)

SCS in the PHN (lack of trials)

Self-management strategies for chronic pain

Prevention

Varicella vaccine to prevent chickenpox which reduces overall incidence and reduces severity of the disease (Zostavax® from Merck seems to reduce the incidence of PHN)

Vaccination above the age of 60 (with live attenuated VZV vaccine) causes a boosting of immunity against VZV

In a double-blind RCT, vaccination of adults aged over 60: reduction of shingles by 61.1% over 3.12 years' surveillance period

Vaccination is recommended to all adults aged over 60 who have had chickenpox or not

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24.10 Meralgia paraesthetica

De nition

Pain, tingling, and numbness felt in the distribution of the lateral cutaneous nerve of the thigh (antero-lateral thigh)

Incidence

In the general population: 4.3 in 10 000 person-years

In people with diabetes: 24.7 per 10 000 person-years

Anatomy

The lateral cutaneous nerve of the thigh arises from the lumbar plexus from contributions from L2 and L3 nerve roots

It runs along the lateral border of the psoas muscle before entering the thigh by passing through the lateral part of the inguinal ligament adjacent to the ASIS (although the course can vary)

The most common cause of meralgia paraesthetica is focal entrapment of the nerve as it passes through the inguinal ligament

Risk factors

Obesity, pregnancy

Wearing heavy tool belts or body armour

Traumatic injury (e.g. seat belt injury, prone surgery)

Rarely, masses within the pelvis can injure the nerve more proximally

The higher incidence in diabetics may indicate that the nerve is more vulnerable due to added metabolic injury

Diagnosis

Diagnosis is made on clinical grounds

Pain, dysaesthesia, and/or paraesthesiae in the nerve distribution (lateral thigh)

Sensory changes are found on examination—hypoaesthesia and/or dysaesthesia are common

Deep palpation just below and medial to the ASIS often elicits the symptoms

The nerve is pure sensory, so motor function is not a ected

Treatment

Address risk factors (tight clothing/belts, obesity, diabetes)

Neuropathic pain medications

Focal LA and steroid nerve blocks—with or without US

Surgical decompression—has been described but is rarely performed

Prognosis

Pain and paraesthesiae usually resolve with time, but numbness may remain

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24.11 Complex regional pain syndrome

De nition

As per IASP, CRPS is a syndrome characterized by continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion

Types

Type 1: minor injuries or fracture of a limb precede the onset of symptoms (fractures, sprains, surgery, immobilization)—90% of cases

Type 2: develops after injury to a major peripheral nerve—10% of cases

NOS: not otherwise speci ed (recent addition to the classi cation)

Impact

Associated with signi cant disability and reduced QoL

Variable progress

Increased health care costs and societal costs

Pathophysiology

Peripheral sensitization

Sympathetically mediated pain (red/warm, cold/blue)

Central sensitization (intense and repeated stimulus leads to hypersensitivity), NMDA receptor-mediated (treatment with ketamine and IV Mg^{2+})

Autoimmune processes (treatment with IV Ig)

Motor and sensory dysfunction

Protective disuse—cortical reorganization sustains CRPS (the limb can feel strange, dis gured, out of place treatment: graded motor imagery)

Aberrant healing and exaggerated in ammation

CRPS due to nerve damage

Epidemiology

Women are 3–4 times more likely to be a ected

Peak incidence between 37 and 50 years

Prevalence: 12–60/100 000 population

85% of patients improve within the rst year

2% recurrence rate

Association with female sex, asthma, migraine, osteoporosis, and intake of ACEIs

Diagnosis (Budapest criteria: signs and symptoms)

1. Continuous pain (which is disproportionate to the inciting event)

2. At least one symptom in three categories of (i) to (iv):

i. Sensory (allodynia = touch is painful; hyperalgesia = hypersensitivity to painful stimulus; hypoaesthesia = reduced sensation)

ii. Vasomotor (temperature, colour changes)

iii. Sudomotor (oedema = swelling; sweating abnormalities)

iv. Motor/trophic changes (weakness, tremor, hair/nail growth changes, skin changes)

3. At least one sign (at evaluation) in two or more categories of (i) to (iv):
   i. Sensory (hyperalgesia to pinprick; allodynia = light touch and temperature are painful; deep somatic pressure; joint movement)
   ii. Vasomotor (temperature asymmetry >1°C, skin colour changes)
   iii. Sudomotor changes/oedema (sweating changes)
   iv. Motor/trophic changes:
      a. Motor: reduced ROM ± motor dysfunction, weakness, tremor, dystonia
      b. Trophic: skin changes, hair and nail growth changes

4. No other diagnosis can better explain the signs and symptoms

CRPS severity score

Self-reported symptoms

Allodynia, hyperpathia (1)
Temperature asymmetry (1)
Skin colour (1)
Sweating (1)
Oedema (1)
Trophic changes (hair, nail, skin) (1)
Motor changes (weakness, tremor, dysfunction) (1)
Reduced ROM (1)

Signs on examination

Hyperpathia to pinprick (1)
Allodynia (touch, brush, cold, warm, vibration, pressure) (1)
Temperature asymmetry (1)
Skin colour (1)
Sweating asymmetry (1)
Oedema asymmetry (1)
Trophic changes (1)
Motor changes (1)
Reduced active ROM (1)

Tests

Thermography (temperature)
Sweat testing
Imaging (X-ray, bone densitometry to check for osteoporosis)
Electrophysiology (EMG)

Treatment

Need a multidisciplinary and multimodal approach
Education (self-management) stroke gently and frequently

Specialized physiotherapy/occupational therapy

Desensitization (rubbing limb), weight-bearing
Stretching, ne motor exercises
Tactile discrimination therapy
Mirror therapy, graded motor imagery (imagined hand movements)

Medication

Anti-neuropathics (nortriptyline/amitriptyline, pregabalin/gabapentin)
Corticosteroids in early CRPS (if onset <6 months), e.g. prednisolone
Bisphosphonates if onset <6 months (to increase bone strength)
Calcitonin
Nifedipine (vasodilator) in cold extremity CRPS
Spasmolytics (in dystonia, tremor, myoclonus): baclofen, BZDs
N-acetylcysteine 600 mg: trial of 3 months (three times per day) blue/white/cold limb
Dimethylsulfoxide (DMSO) cream: trial of 3 months (ve times per day)—hot/warm/swollen limb
Ketamine (low dose)

Injections

Stellate ganglion block (injection in the neck for arm symptoms)
T2–3 sympathetic block for upper limb CRPS resistant to stellate ganglion block
Lumbar sympathetic block (injection in the lower back for leg symptoms)
Peripheral nerve blocks (for arm and leg symptoms)
Epidural and IT therapy
SCS (spinal cord stimulators are recommended by NICE and their long-term e ect is under evaluation)

Defer elective operations in early CRPS until symptoms subside.

For ongoing pain

Physiotherapy, psychological support, and doctor appointments
Self-support groups
Leisure and social activities

Other supportive therapies

CBT (specialized centres)
Education of health care professionals about CRPS (e.g. GPs)
Patient-centred approach and facilities in place to request top-up support
EEG biofeedback
Psychotherapy
Relaxation techniques, hypnosis

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24.12 Phantom limb and stump pain

De nition

Removal or amputation of a part of the body such as a limb, breast, or other, usually resulting in an awareness of phantom sensations in the amputated part—can range from a feeling of the part being present to severe pain

Types

Phantom awareness: a feeling of the missing part being present

Phantom sensation: any speci c sensation of the missing limb, except pain, e.g. paraesthesiae, speci c position or shape

Phantom pain: painful, unpleasant sensations in the distribution of the missing limb—can be cramping, burning, shock-like, sharp, or dull pain

Stump pain: pain referred to the residual stump, unlike phantom pain

Stump contractions: spontaneous movement of the stump, ranging from small jerks to visible contractions

Telescoping: this is retraction of the phantom part sensation towards the residual stump

Incidence

85% of amputees experience phantom sensations in the initial weeks after amputation

60–80% of amputees experience phantom pain. However, substantially fewer patients (5–10%) experience severe pain

Lower in young children

More frequent in upper limb amputees

Lasts from a few weeks to many years. In many of the cases, it gradually reduces in severity

Risk factors

Uncontrolled pre-amputation pain and persistent perioperative/stump pain

Psychological factors, such as anxiety, depression, and lack of social support, play a role

Genetic predisposition

Diagnosis

Mainly history

Phantom pain

Onset: within the rst few weeks of an amputation, but in a small number of cases, it may develop months to years after an amputation

Site: usually experienced in the distal parts of the limbs in limb amputees. Amputation of another part (e.g. breast) results in pain in that region

Timing: usually intermittent, rather than constant. Frequency can vary from every day to weekly

Quality: shooting, burning, aching, pins and needles, cramping

Stump pain

Onset: common in the early post-amputation period but can persist beyond the surgical healing stage

Site: on the residual stump

Quality: throbbing, burning, stabbing, spontaneous movements

Examination findings: areas of hypoaesthesia, hyperalgesia, or allodynia

60% of amputees with phantom pain have coexisting stump pain

Examination/investigations

Skin for erythema, temperature, allodynia, neuroma, and infection

X-ray, US, and MRI to look for pathology

Wound swabs for infection

Heterotropic ossification in >60% of trauma amputations where there is a deposit of Ca^{2+} in the stump. Can be see on X-ray

Pathophysiology

Not completely understood

Changes occur at the peripheral, spinal, and supra-spinal levels

Peripheral mechanisms

Peripheral sensitization occurs

Neuromas after amputation can show spontaneous abnormal activity and sensitivity that can cause phantom and stump pain

Cell bodies in the *DRGs* also show similar abnormal activity

Cross-talk of the sympathetic and sensory nervous systems at the level of the DRGs contributes to the increased pain response following a change in sympathetic activity

Spinal mechanisms

Central sensitization occurs because of an increase in sensitivity and abnormal activity in DH neurons, expansion of the receptive field, and increased activity in the NMDA receptor complex

Supra-spinal mechanisms

Cortical reorganization plays an important role in the development of phantom pain

The somato-sensory cortex of the amputated part starts receiving sensory input from the adjacent areas

This abnormal input may result in amplification of sensation and pain

Normally dormant thalamic neurons also start to respond to stimuli

Management

High-quality evidence for treatment of phantom and stump pain is lacking

General guidelines for treatment of neuropathic and nociceptive pain should be followed

Management of phantom and stump pain is not very effective and is challenging

Prevention

Epidural infusion ideally instituted before amputation (good result, but may not be practical)

Prolonged perineural infusion of LA (very good analgesia and may prevent phantom pain)

Ketamine perioperative bolus and infusion

Memantine PO at 5 mg, maximum 20 mg/day

Gabapentinoids perioperatively reduces opioid consumption but may not prevent phantom pain

Multimodal, multidisciplinary, pragmatic perioperative pain management pathway involving the inpatient pain team (see Fig. 24.12.1)

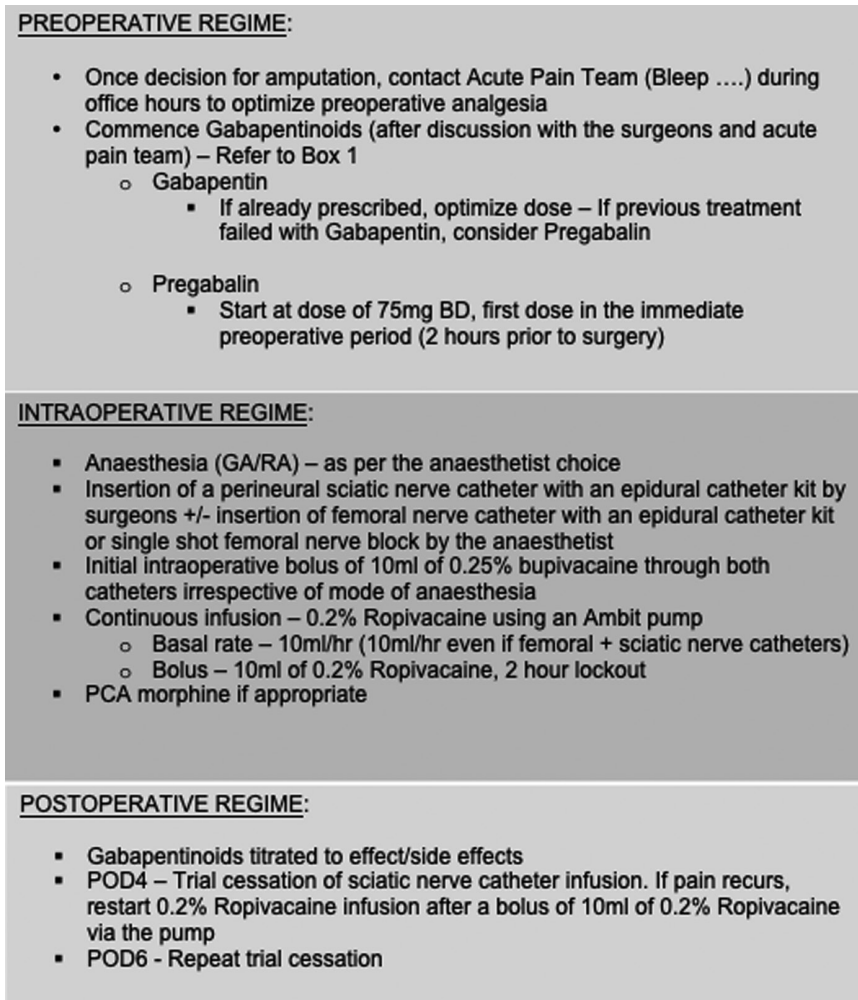


Figure 24.12.1 Sample of a multimodal perioperative pain management guideline

Reproduced from Aladin, H., Jennings, A., Hodges, M., and Tameem, A. (2018). Major lower limb amputation audit – introduction and implementation of a multimodal perioperative pain management guideline. *British Journal of Pain*, 12(4):230–237. http://doi.org/10.1177/2049463718769339

Early stump pain

Should be treated with paracetamol, NSAIDs, and opioids with neural blockade if appropriate
If neuropathic features are present, then TCAs and gabapentinoids should be instituted
TENS—some evidence of its use in acute cases
Baclofen, especially if stump contractions present

Acute phantom pain

Salmon calcitonin:

- Neuropeptide hormone
- Alters -endorphin, inhibits PG and cytokine production, and modulates central serotonergic pathways
- SC for 5–7 days (100 IU/day)

Chronic stump and phantom pain

Pharmacological treatment:

- Anti-neuropathic agents—amitriptyline, gabapentin (moderate-quality evidence)
- Anticonvulsants—carbamazepine, lamotrigine (for lancinating pain)
- Opioids—morphine, tramadol (both have been shown to be bene cial)
- NMDA antagonists—IV ketamine over 1 hour reduces phantom pain
- Other drugs—calcitonin, capsaicin, lidocaine plasters, IT opioids (no good-quality evidence for these drugs)
- Capsaicin 8% patches (Qutenzas®)—reduction in pain and stump hypersensitivity, enabling wearing stump prosthesis

Interventions

Stump revision can be performed if there is stump pathology
Neuroma excision
Excision of Ca^{2+} deposits in heterotropic ossi cation
SCS and dorsal root entry zone lesioning have had disappointing results
Botulinum toxin injections have improved phantom pain

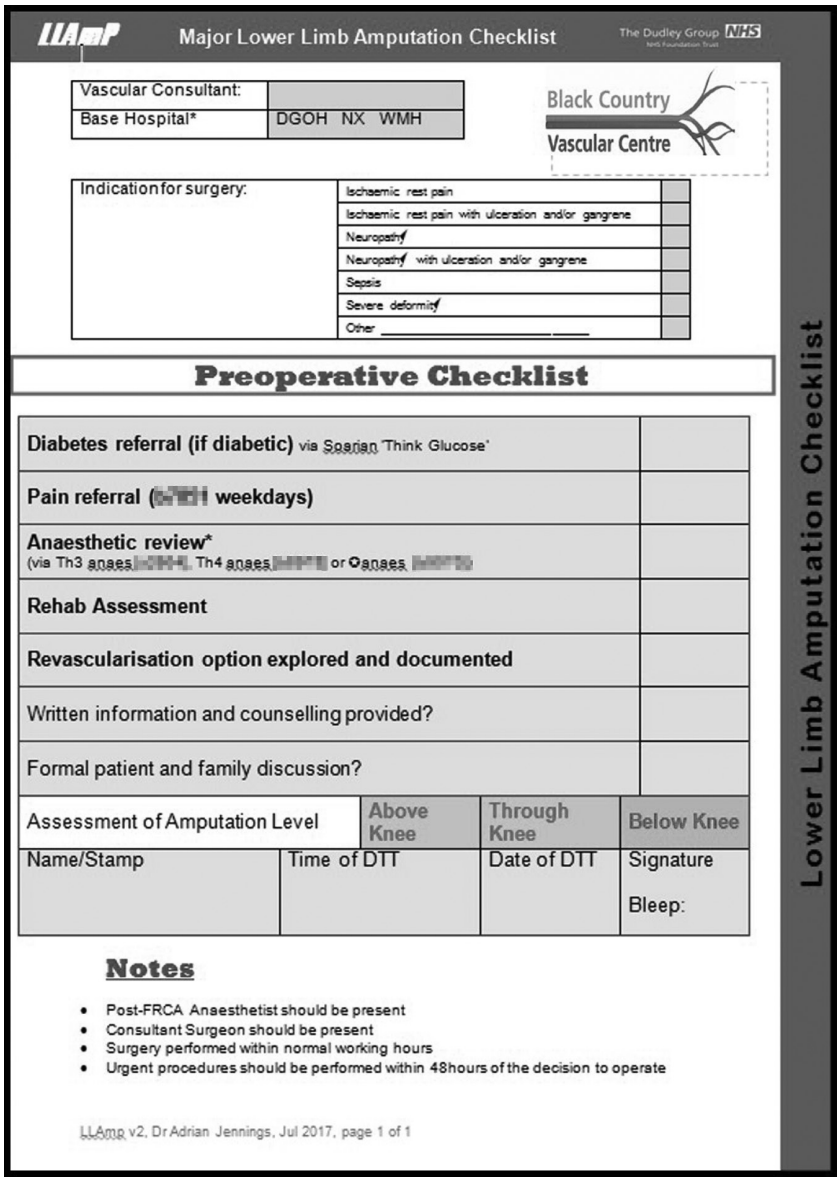
Psychological interventions

Education, CBT, biofeedback, and hypnosis reduce severity of pain (low-quality evidence)

Other treatments

Graded motor imagery (laterality, imagery, mirror therapy)
TENS
Physiotherapy, OT, and desensitization
Prosthetics

Sample of a checklist used for major lower limb amputations in vascular surgery (see fig 24.12.2)



LLAmP Major Lower Limb Amputation Checklist — The Dudley Group NHS

Vascular Consultant:	
Base Hospital*	DGOH NX WMH

Black Country Vascular Centre

Indication for surgery:	
	Ischaemic rest pain
	Ischaemic rest pain with ulceration and/or gangrene
	Neuropathy
	Neuropathy with ulceration and/or gangrene
	Sepsis
	Severe deformity
	Other _____

Preoperative Checklist

Diabetes referral (if diabetic) via Soarian 'Think Glucose'	
Pain referral ([redacted] weekdays)	
Anaesthetic review* (via Th3 anaes[redacted], Th4 anaes[redacted] or Oanaes[redacted]	
Rehab Assessment	
Revascularisation option explored and documented	
Written information and counselling provided?	
Formal patient and family discussion?	

Assessment of Amputation Level	Above Knee	Through Knee	Below Knee
Name/Stamp	Time of DTT	Date of DTT	Signature Bleep:

Notes

- Post-FRCA Anaesthetist should be present
- Consultant Surgeon should be present
- Surgery performed within normal working hours
- Urgent procedures should be performed within 48hours of the decision to operate

LLAmp v2, Dr Adrian Jennings, Jul 2017, page 1 of 1

Lower Limb Amputation Checklist

Figure 24.12.2 Sample of a checklist used for major lower limb amputations (vascular)

Reproduced from Aladin, H., Jennings, A., Hodges, M., and Tameem, A. (2018). Major lower limb amputation audit – introduction and implementation of a multimodal perioperative pain management guideline. *British Journal of Pain*, 12(4):230–237. http://doi.org/10.1177/2049463718769339

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24.13 Diabetic polyneuropathy

De nition

Diabetic neuropathy is a type of nerve damage in diabetic patients without any other demonstrable causes of peripheral neuropathy

High blood sugar levels can cause injury in nerves throughout the body, but most frequently in the legs and feet

It is a common complication of diabetes but can often be prevented or slowed with tight blood sugar control and a healthy lifestyle

It may or may not be painful

Types of diabetic neuropathy

Several classi cations—based on anatomical distribution (two main types)

Di use or generalized symmetrical neuropathy (most common)

Chronic distal sensorimotor polyneuropathy (in feet/legs, then hands/arms)—most common cause of painful diabetic neuropathy. Pain a ects QoL in 56% of these patients

Acute sensory neuropathy

Autonomic neuropathy—cardiovascular, GI, and genitourinary systems

Focal mononeuropathy (damage to a speci c nerve) or multifocal neuropathy

Cranial—face

Truncal

Focal limb neuropathy (usually in legs)

Proximal neuropathy (diabetic amyotrophy) in thighs, hips, buttocks, and legs (sensory and motor systems can be a ected)

Chronic in ammatory demyelinating polyneuropathy—in ltration of in ammatory cells causes damage to myelin sheaths and vasa nervosum

Epidemiology and incidence

Incidence and prevalence are di cult to verify (no consistent diagnostic criteria in studies)

One-third of diabetic patients su ered from painful neuropathy (large community study in England)

>50% of patients with chronic distal sensorimotor polyneuropathy complain of pain a ecting their QoL

Prevalence of chronic distal sensorimotor neuropathic polyneuropathy in type 1 diabetes is 5%, while in type 2 diabetes, it is 15–20%

Incidence: men = women

The incidence of non-painful versus painful diabetic polyneuropathy is higher

Pathophysiology (three theories)

Polyol pathway

Conversion of excessive intraneural glucose to sorbitol and fructose via polyol pathway
This causes reduced Na-K-ATPase activity, thus reduced production of NO and glutathione (vasodilators and bu er against oxidative injury), leading to chronic ischaemia

Microvascular damage theory

Neural ischaemia due to endothelial hyperplasia and thickening of the basal membrane

Glycosylation end-product theory

Reduced axonal transport in chronic hyperglycaemia, leading to accumulation of oxidative end-products around peripheral nerves, resulting in oxidative stress and damage

Other contributors to nerve injury

Abnormal Ca^{2+} channel function and Na^{+} channel activity (role in painful neuropathy)

Risk factors

Poor diabetic control (most important factor)
Duration of diabetes
Old age
Overweight
Dyslipidaemia (increased low-density lipoprotein or triglycerides)
Hypertension
Coexisting: kidney damage, smoking/alcohol
Genetic predisposition

Symptoms

Some with mild symptoms
Can be quite painful and disabling

Distal symmetrical painful neuropathy

Gradual onset, normally starts with sensory symptoms
At the beginning, patients commonly have distal symmetrical burning or aching pain, which spreads proximally over time
Length-dependent diabetic neuropathy (a ects longer nerves rst), involving the feet and legs in a stocking distribution
Upper limb (hands/arms—glove distribution) may be involved in more severe cases
Often worse at night
Numbness (reduced pain/temperature sensation), tingling, burning, sharp, cramps, allodynia (pain on walking/standing/touching clothes), muscle weakness, loss of re exes (ankle), loss of balance, foot ulcers/infections, bone and joint pain

Autonomic neuropathy

Hypoglycaemia unawareness
Bladder problems (infections, retention, incontinence)
Constipation/diarrhoea or both
Gastroparesis (nausea, vomiting, bloating, loss of appetite)

Swallowing, sweating, and body temperature may be a ected
Accommodation of eyes a ected
Tachycardia at rest, postural hypotension
Erectile dysfunction, vaginal dryness, reduced libido

Proximal neuropathy (diabetic amyotrophy)

More common with type 2 diabetes and older adults
Usually one-sided, but can spread to the other side of the body
Severe pain in hip, thigh, and buttock area
Weak, shrinking thigh muscles
Di culty rising from sitting position
Weight loss
Abdominal swelling is possible

Focal neuropathy (mono-neuropathy)

Damage to a single nerve in the face, trunk, and legs
More common in the elderly
Can cause sudden, severe pain which usually goes away after weeks/months without treatment
Pain in the shin/foot, anterior thigh, lower back, pelvis, chest, and abdomen
Bell's palsy (one-sided facial paralysis)
Eye (double vision, di culty focusing, ache behind the eye)
Carpal tunnel syndrome due to nerve compression

Diagnosis (exclusion of other factors)

Clinical history (symptoms)

Burning pain, allodynia
Sharp electric, current-like sensations
Paraesthesiae, hyperaesthesia, and deep aching pain
Pain usually worst at night, lower limbs more a ected than upper limbs
ANS involvement, particularly in long-standing diabetes (tachycardia, orthostatic hypotension, sexual dysfunction, altered gut motility, and loss of gastro-oesophageal function)

Neurological examination

Loss of touch and pin prick pain sensation (early), lament test
Loss of proprioception
Loss of vibration sense
Absent ankle re ex
Gait ataxia
Signs of peripheral autonomic dysfunctions in peripheries (e.g. cold feet, engorged veins)

Neuropathic pain questionnaires

DN4, NPS, LANSS, NPSI, NPQ

Speci c investigations

NCS/EMG—detect large myelinated nerve dysfunction (,); cannot detect small bre polyneuropathies (A-delta, C)

Blood tests: sugar levels, HbA1c (glycosylated haemoglobin, e.g. twice per year)

QST (vibration, temperature)—an increased sensory threshold correlates with sensory loss, and lowered thresholds with allodynia/hyperalgesia

Autonomic function testing (supine and postural BP, sweating tests)

Skin testing for epidermal nerve fibre density and morphology

Differential diagnoses

Peripheral vascular disease

Morton's neuroma

Vitamin B12 deficiency

Malnutrition

Hypothyroidism

Uraemia

Restless legs syndrome

Neuropathy from toxins, e.g. alcohol

Management/treatment

Education—lifestyle modification (healthy diet, exercise, stopping smoking/drinking alcohol)

Optimal glycaemic control (between 4.4 and 7.2 mmol/L before meals, below 10 mmol/L 2 hours after meals

Care of diabetic ulcers

Management of cardiovascular risk factors

Pain management (symptomatic)

Pharmacological pain management

Tricyclic antidepressants

Amitriptyline (NNT = 3.5)—increased risk of sudden cardiac death if >100 mg/day

Serotonin–noradrenaline reuptake inhibitors

Good for coexisting depression

First line is duloxetine—no significant difference between 60 mg once daily and 60 mg twice daily (both doses better than placebo)

Venlafaxine NNT 4.5 for 150–225 mg of extended-release formulations

Antiepileptics

Also useful in generalized anxiety disorder

Gabapentinoids (pregabalin, gabapentin) bind to -2 delta-1 subunit of Ca^{2+} channels, resulting in reduced release of excitatory neurotransmitters

Evidence is weak for lamotrigine, topiramate, and carbamazepine

Note: pregabalin facilitates sleep; duloxetine increases sleep fragmentation and reduces the rapid eye movement phase of sleep

Intravenous lidocaine infusion

For further information, see 6.2 Lidocaine, p. 104

Topical capsaicin

Focal treatment with capsaicin 0.025 or 0.075%, Qutenza® (8% capsaicin patches) 2–3 times per year (see 13.6 Capsaicin, p. 240)

Non-pharmacological pain management

CBT, ACT, multidisciplinary pain management

TENS, acupuncture (limited evidence)

SCS (RCT showed reduced pain and improved QoL with refractory painful diabetic neuropathy in the lower extremities)

Management of complications

Loss of toe, foot, or leg (infections, ulcers) check feet daily; dry, clean, trimmed toenails

Joint damage (Charcot joint)—surgical and non-surgical management

Recurrent urinary infections and urinary incontinence (medication, strict schedule, self-catheterization)

Hypoglycaemia (reduced awareness due to autonomic changes)—check blood sugar levels regularly

Orthostatic hypotension (drink plenty of water, get up slowly, medication, sleep with head up, compression stockings)

Digestive problems (eat smaller, more frequent meals; reduce bre and fat; eat soups/pureed food; change diet for constipation, diarrhoea, and nausea)

Sexual dysfunction (some medications, vacuum devices in men, lubricants in women)

Increased or decreased sweating

Further reading

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2. Haanpää M, Hietaharju A. Halting the march of painful diabetic neuropathy. International Association for the Study of Pain. Pain: Clinical Updates 2015;Vol. XXIII (No. 2)
3. Mayo Foundation for Medical Education and Research. Diabetic neuropathy. March 2020. https://www.mayoclinic.org/diseases-conditions/diabetic-neuropathy/symptoms-causes/syc-20371580
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24.14 Charcot–Marie–Tooth syndrome

Introduction

Charcot-Marie-Tooth syndrome (CMT) syndrome is a spectrum of inherited disorders caused by mutations of genes that are expressed in peripheral nerves (axons and/or myelin)

Includes over 30 di erent disorders, the most common being types 1 and 2 and the primary X-linked form

Autosomal dominant condition

Rate of disability generally increases with age, with considerable variability, depending on the CMT subtype, age of onset, and clinical severity

Clinical features

CMT disease type 1

Demyelinating sensorimotor neuropathy

Several types—CMT1A and CMT1B are the most common

CMT1A, the most common mutation, is a duplication of the peripheral myelin protein gene on chromosome 22

Onset typically in the first two decades of life

Presents normally with walking difficulties and ankle sprains from:

- Muscle weakness initially in leg calves. Distal wasting may produce the classical inverted champagne bottle deformity
- Sensory loss: gradual, normally involves proprioception and vibration sense
- Later changes: atrophied intrinsic muscles of the hands and feet
- Pes cavus foot and kyphoscoliosis are normally associated
- Sometimes there are palpable thickening of peripheral nerves
- Life expectancy not affected

CMT disease type 2

Axonal sensorimotor neuropathy—demyelination does not normally occur

Onset in the second decade or later

Sensory symptoms (decreased proprioception and vibration sense) are more marked than motor symptoms

Usually there is areflexia in the legs only

Structural deformities are not common

Nerve conduction is slow, but always >38 m/s

There is no palpable thickening of peripheral nerves

Management

Specific treatment for CMT is currently unavailable

Exclude other neuropathies (e.g. diabetes, immune-mediated, nutritional, etc.)

Multidisciplinary interventions as per chronic pain management principles to improve function and well-being:

- Physical treatments: strengthening, stretching, endurance, orthotics
- Psychological treatments: CBT, ACT, cognitive restructuring, distraction, relaxation, mindfulness
- Pharmacotherapy can be considered: TCAs, gabapentinoids, or SNRIs

Avoid drugs that exacerbate the weakness and/or may harm the patient:

- Definite risk: vinca alkaloids (vincristine), taxols (paclitaxel, docetaxel, cabazitaxel)
- Moderate/significant risk: amiodarone, cisplatin, colchicine, fluoroquinolones
- Minor risk: 5-fluorouracil, adriamycin, chloroquine, griseofulvin, hydralazine
- Negligible risk: allopurinol, amitriptyline, chloramphenicol, clofibrate

Alcohol is not a neurotoxic drug but affects balance and coordination, and overconsumption of alcohol is generally not recommended

Surgery may be indicated to improve pain, function, and significant deformities associated with CMT such as:

- Osteotomy—severe pes at feet
- Arthrodesis—severe pes at feet and correcting heel deformities

Plantar fascia release—persistent heel pain from in amed tendons

Spinal surgery—scoliosis causing severe functional impairment

Research of new treatments:

Stem cells (cells at an early stage of development) to repair nerve damage

Hormonal and gene therapy to slow progression of CMT

Ascorbic acid has been used in some trials

Further reading

1. Kang PB. Charcot–Marie–Tooth disease: genetics, clinical features and diagnosis. 2020. https://uptodate.com
2. Kang PB. Charcot–Marie–Tooth disease: management and prognosis. 2020. https://uptodate.com.

CHAPTER 25

Rheumatological Conditions

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25.1 Biomarkers and investigations in rheumatology

In ammatory markers (ESR and CRP)

ESR is an indirect measure of in ammatory response

CRP is produced by the liver during an in ammatory response

ESR and CRP can be increased in infection, in ammation, malignancy, and tissue injury

ESR and CRP discrepancy can be due to di erence in kinetics, with CRP rising and decreasing more rapidly than ESR

ESR and/or CRP are usually elevated in patients with polymyalgia rheumatica, giant cell arteritis, vasculitides, and acute crystal arthropathy (vasculitides are a heterogenous group of autoimmune diseases, characterized by in ammation of blood vessels (vasculitis) and subsequent ischaemia and organ damage)

ESR and/or CRP may, or may not, be increased in patients with RA and seronegative spondyloarthritis

ESR and CRP are not increased in patients with OA or joint hypermobility syndrome

Patients with SLE can have isolated elevation of ESR without an increase in CRP

Serum uric acid

It is possible to have elevated serum uric acid without having gout

Uric acid crystals should be present in synovial uid to con rm diagnosis

Immunological tests

Both rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibody should be tested in patients with suspected RA

Patients with RA can test positive for anti-CCP antibody, rheumatoid factor, both antibodies, or neither antibody

Anti-CCP is more speci c, but rheumatoid factor is more sensitive

High titre of rheumatoid factor is a better predictor for severe disease with extra-articular manifestations

Anti-nuclear antibodies (ANA) are present in 3–15% of the healthy population

ANA are present with varying frequency in patients with SLE, scleroderma, Sjögren's syndrome, polymyositis/dermatomyositis, mixed connective tissue disease, drug-induced lupus, juvenile in ammatory arthritis, and autoimmune hepatitis

Patients with suspected connective tissue diseases are further characterized according to clinical features and the presence of other autoantibodies (anti-double-stranded DNA (dsDNA), anti-Ro, anti-La, anti-Sm, anti-RNP, anti-phospholipid, anti-centromere antibodies, anti-Scl-70)

Creatine kinase (CK) should be measured if myositis suspected

Measurement of complement activation (C3 and C4) can be useful in patients with SLE

Anti-neutrophil cytoplasmic antibodies (ANCA) are frequently found in patients with granulomatosis with polyangitis, microscopic polyangitis, and eosinophilic granulomatosis with polyangitis, which are collectively known as the ANCA-associated vasculitides

Any patient with suspected connective tissue disease or vasculitis must have urinalysis to look for haematuria and proteinuria

Imaging

X-rays show characteristic changes in patients with long-standing rheumatic diseases (ankylosing spondylitis, gout, RA, and OA)

US with power Doppler is used to detect synovitis in early in ammatory arthritis

MRI with gadolinium enhancement, or MRI (T1 and STIR) is also used to detect early in ammatory arthritis in peripheral joints and the spine, respectively

Further reading

1. Bijlsma JWJ, Hachulla E. EULAR Textbook on Rheumatic Diseases. 2nd edition, 2015. London: BMJ Publishing Group Ltd
2. American College of Rheumatology. https://www.rheumatology.org
3. UpToDate. https://www.uptodate.com

25.2 Ankylosing spondylitis

De nition

The term **ankylosing spondylitis (radiographic axial spondyloarthritis)** is reserved for patients with spinal symptoms and X-ray changes of sacroiliitis

Patients often have other manifestations (enthesitis 40–60%) and/or acute anterior uveitis (30–50%)

The term **non-radiographic axial spondyloarthritis** (nr-ax SpA) is used for patients with symptoms of in ammatory back pain (insidious onset, pain at night, age at onset <40 years, improvement with exercise but not with rest) without sacroiliitis on X-rays, although 70% have visible in ammation in the SIJs and/or the spine when MRI of the whole spine and SIJ (T1 and STIR) is done

Axial spondyloarthritis (radiographic and non-radiographic) is also found in patients with psoriatic arthritis, in ammatory bowel disease (ulcerative colitis and Crohn's disease), reactive arthritis, and juvenile spondyloarthritis.

Prevalence

0.2–0.5% (this varies according to the prevalence of the HLA-B27 gene in di erent ethnic groups)

The chance of developing ankylosing spondylitis in HLA-B27-positive patients is 1–5%; it increases to 15–20% in the case of an a ected rst-degree relative

Pathophysiology

Aetiology is unknown

Thought to re ect a complex interplay of genetic and environmental factors

In ammation a ecting SIJs, entheses, vertebral bodies, peripheral joints, GI tract, and the eyes

Diagnosis

It is suspected in patients with symptoms of in ammatory back pain and con rmed by X-ray (ankylosing spondylitis), or alternatively by specialized MRI (patients with nr-ax SpA)

Usually diagnosed by a rheumatologist, or referred to rheumatology services shortly after diagnosis

Treatment of early disease

1. **Education** about diagnosis and prognosis
2. Importance of **exercise** to help symptoms and maintain posture, ROM, and aerobic tness. Referral to physiotherapists and patient support groups (National Ankylosing Spondylitis Society (NASS))
3. Strongly advised to **stop smoking**
4. NSAIDs and **simple analgesics**
5. **Injection** of SIJs with corticosteroid (image-guided)
6. Injection of costochondral joints, peripheral joints, entheses, and plantar fascia if required
7. **Ongoing assessment** of patients using standard scores such as BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and BASFI (Bath Ankylosing Spondylitis Functional Index), measuring ROM
8. Identi cation of patients not responding to NSAIDs and exercise—for treatment with **biologic medication (TNF alpha inhibitor or other agent)**
9. Biologic medication prescribed by a rheumatologist (national guidance)
10. **Conventional disease-modifying anti-rheumatic medication** (cDMARD) such as sulfasalazine, methotrexate, or le unomide if there is peripheral arthritis
11. **Advice** with regard to workplace, conception, and pregnancy
12. **Ongoing monitoring** for complications of disease or treatment

Treatment of long-standing disease

1. Assessment to distinguish mechanical problems (xed rigid spine, osteoarthritic hips and shoulders) from **ongoing in ammatory problems**
2. **Further investigations** if spinal fracture (this can occur after minor trauma in patients with rigid osteoporotic spines), spinal instability, or spinal stenosis suspected
3. **Management of in ammatory disease**, as for early disease
4. **Surgical referral**, if required, for shoulder and hip disease
5. Diagnosis and treatment of **coexisting osteoporosis**
6. **Ongoing surveillance** for aortic regurgitation, risk factors for IHD and apical pulmonary brosis
7. Appropriate **exercise** regimes for established disease
8. **Environmental modi cations** to help with physical limitations due to loss of spinal mobility (prism spectacles, large driving mirrors, domestic aids and appliances)

9. Adequate **pain relief** (paracetamol, occasionally opioids and anti-neuropathics)
10. Occasionally facet joint injection (if thought to be source of pain)

Further reading

1. Bijlsma JWJ, Hachulla E. EULAR Textbook on Rheumatic Diseases. 2nd edition, 2015. London: BMJ Publishing Group Ltd
2. National Axial Spondyloarthritis Society. http://nass.co.uk/

25.3 Gout

De nition

Gout is a monosodium urate (MSU) crystal deposition disease

Prevalence

3% of the population

Male:female ratio 20:1

Increasing prevalence linked to increased longevity, age-associated cardiovascular, metabolic, and renal disease, medications, and increased consumption of foods that contribute to obesity and diabetes mellitus

Pathophysiology

Serum uric acid (SUA) levels are in uenced by the total amount of SUA produced, renal clearance of urate, and intestinal excretion of urate

Release of MSU crystals results in an intense in ammatory response involving neutrophils, monocytes/macrophages, and lymphocytes

Joints most often a ected are the feet, ankles, and knees, although Achilles tendons, olecranon bursae, wrists, and metacarpophalangeal (MCP) and proximal interphalangeal joints can also be involved

Diagnosis

Usually presents as episodes of acute monoarthritis (podagra = gouty arthritis in the metatarsophalangeal joint of the big toe has high speci city >97% and sensitivity >96%)

Tophi occur in long-standing undertreated gout and represent deposits of MSU crystals

Identi cation of MSU crystals in synovial uid from joints (needle aspiration) during an acute attack (speci city: 100%, sensitivity: 84%), asymptomatic joints during inter-critical periods, or tophi allows a de nitive diagnosis

Blood test: elevated serum uric acid > 6mg/dL (normal range: 3-8 mg/dL or 0.18-0.48 mmol/L, but age and gender di erences) low sensitivity: 67% and speci city: 78%)

'Punched-out' erosions with sclerotic margins and overhanging edges in a marginal and juxta-articular distribution on X-rays

US to identify the characteristic 'double contour sign' in articular cartilage, erosions, and tophaceous deposits

Treatment

1. Management of gout is often suboptimal, leading to undertreated patients with ongoing symptoms

2. Acute attacks managed with low-dose **colchicine** (0.5 mg three times daily), NSAIDs, intra-articular steroid, or PO steroids
3. **Allopurinol** is started at a low dose (100 mg daily), and titrated upwards in 100 mg increments, every few weeks, until SUA <300 micromoles/L (allopurinol dose reduced in patients with renal dysfunction)
4. Patients often need treatment with low-dose colchicine, **NSAIDs**, **or low-dose steroids** for the first 3–6 months of treatment with any urate-lowering medication
5. **Febuxostat** can be used in patients with renal insufficiency or intolerance of allopurinol, but it is avoided in patients with IHD or heart failure
6. **Benzbromarone** is an effective uricosuric drug, which can be used in patients with mild to moderate renal impairment or who are refractory to allopurinol. Specialist use on a named-patient basis only in many countries
7. **Losartan and fenofibrate** have modest SUA-lowering effect and can be used as co-adjuvants in patients also requiring treatment for hypertension and hyperlipidaemia
8. Patients should be given **lifestyle advice** (maintaining healthy BMI, avoiding large quantities of shellfish, offal, and sugar-sweetened soft drinks, and reducing alcohol intake in line with national guidance)
9. Cardiovascular risk factors should be addressed, as gout is independently associated with risk of MI

Further reading

1. Bijlsma JWJ, Hachulla E. EULAR Textbook on Rheumatic Diseases. 2nd edition, 2015. London: BMJ Publishing Group Ltd
2. Hui M, Carr A, Cameron S, et al. for the British Society for Rheumatology Standards, Audit and Guidelines Working Group, The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology, Volume 56, Issue 7, July 2017, p. e1–e20. http://academic.oup.com/rheumatology/article/56/7/e1/3855179
3. Gaffo AL, Dalbeth N, Romain PL. Clinical manifestations and diagnosis of gout. UpToDate. 2019 https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-gout
4. Zhang W, Doherty M, Pascual E et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65:1301–11

25.4 Joint hypermobility syndrome

Prevalence

10–20% of the population have joint hypermobility

10–20% of those with joint hypermobility report additional symptoms of fibromyalgia, GI disturbance, bladder symptoms, and autonomic dysfunction

This is sometimes referred to as joint hypermobility syndrome (JHS), although there is debate about whether this is a discreet entity from fibromyalgia/chronic widespread pain

Pathophysiology

Lack of well-defined biologic marker contrasts with other hereditary conditions of connective tissue (Marfan's syndrome, osteogenesis imperfecta, Ehlers–Danlos syndrome (EDS)—classic type or vascular type)

Diagnosis

Joint hypermobility is ascertained if a patient scores 4 points using the Beighton score for hypermobility:

- Passive apposition of thumb to forearm (2 points)
- Passive dorsi exion of fth MCP joint (2 points)
- Hyperextension of the elbow (2 points)
- Hyperextension of the knee (2 points)
- Flexion of lumbar spine with the hands at on the oor (1 point)

The Brighton criteria (1998) can be used to screen patients for JHS

Diagnosis is usually based on clinical features without additional testing. Thought to be indistinguishable from EDS-hypermobility type (previously referred to as EDS type III)

Occasional need for cardiovascular investigations, ophthalmology review, skin biopsy, or genetic testing if features of Marfan's syndrome, EDS-classic type, or EDS-vascular type

Treatment

1. **Physiotherapy** with emphasis on self-management, speci c advice as required, for localized issues (joint subluxation, soft tissue problems)
2. **Holistic care** with advice on symptom management to avoid referral to multiple specialties
3. **Reassurance and psychological support** as association with anxiety and depression
4. Input from **OT** with regard to workplace or ADL
5. Pain managed with **simple analgesics** and short courses of NSAIDs
6. **Multidisciplinary approach** if features of chronic widespread pain/ bromyalgia
7. **Referral to specialist services** if symptomatic orthostatic hypotension or postural tachycardia syndrome
8. Urological or gastroenterology advice if bladder symptoms (dysuria, frequency) or bowel symptoms (re ux, irritable bowel symptoms) not controlled with usual measures
9. Reports of reduced response to LAs in some patients with JHS

Further reading

1. Hakim AJ, Grahame R, Norris P, et al. Local anaesthetic failure in joint hypermobility syndrome. J R Soc Med 2005;98(2):84–5
2. UpToDate. https://www.uptodate.com

25.5 Osteoporosis

De nition

Osteoporosis is a generalized bone disease, characterized by decreased bone mass and deterioration of bone microarchitecture, resulting in increased fracture risk

Osteoporosis does not cause pain. Pain occurs acutely with fragility fractures. Vertebral fractures can be associated with chronic spinal pain, reduced QoL, and reduced life expectancy

Prevalence

In Caucasian populations, 50% of women and 20% of men over the age of 50 will experience a fragility fracture in their remaining lifetime

Pathophysiology

Increased risk of fracture is associated with low peak bone mass, old age, sex steroid de ciency, lipid oxidation, decreased physical activity, use of steroids, and a propensity to fall

Low bone mass may be secondary to underlying disease

The following investigations may be required: FBC, ESR, urea and electrolytes, LFTs, bone pro le, 25-hydroxyvitamin D, thyroid-stimulating hormone (TSH), coeliac screen, testosterone, serum and urine immunoelectrophoresis, 24-hour urinary Ca^{2+}, 24-hour urinary cortisol

Diagnosis

Diagnosis can be made clinically (patients with vertebral fragility fracture or patients >75 years with low trauma impact fracture) without the need for bone mineral density (BMD) measurement

In other patients, BMD measurement is combined with validated risk factors for fracture to give a treatment intervention threshold (e.g. FRAX® = Fracture Risk Assessment Tool)

For epidemiological purposes, osteoporosis has been de ned as a BMD of >2.5 SDs below the mean peak BMD in healthy adults of the same gender, which is expressed as T-score < 2.5 (see Bone density scan (DEXA scan = Dual-Energy X-ray Absorptiometry) in 1.7 Investigations in pain medicine, p. 22)

Any patient with a vertebral fragility fracture as an incidental nding should be investigated for underlying disease and o ered treatment

Management of acute vertebral fracture

1. Can be asymptomatic or painful (6–12 weeks)
2. Pain usually treated with **paracetamol, ibuprofen, naproxen, or co-codamol**
3. **Tramadol and opioids** may be needed
4. **Calcitonin** daily or on alternate days can be given for 2–4 weeks
5. **Vertebroplasty or kyphoplasty** can be used if pain, due to recent unhealed fracture, not controlled by analgesics (see 22.9 Vertebroplasty, p. 438)
6. **Malignancy needs to be excluded** as a cause of acute vertebral collapse
7. All patients with osteoporotic vertebral collapse need to commence appropriate **long-term treatment** in accordance with local pathways (PO and IV bisphosphonates: alendronic acid, risedronate sodium, IV zoledronic acid; human monoclonal antibodies: denosumab; parathyroid hormone analogue: teriparatide)
8. **All treatments are given in conjunction with calcium and vitamin D supplementation**
9. **Education** about the need for long-term medication, and follow-up to check adherence
10. **Physiotherapy and OT** to restore functional status

Management of chronic vertebral fracture

1. Some patients su er chronic pain as a result of spinal deformity
2. May need regular oral analgesia such as **paracetamol, opioids, and/or anti-neuropathics**
3. **Change osteoporosis** medication if evidence of progressive vertebral collapse
4. **Psychological support** to help with problems associated with spinal deformity
5. **Environmental and workplace modi cations** to help with physical limitations
6. **Occasional use of facet joint injection** if secondary OA thought to be source of pain (systemic absorption is low, with minor impact on osteoporosis; consider LA alone or LA with low-dose steroid, particularly in frail/elderly patients)

Prevention of osteoporosis

Healthy balanced diet (high in calcium)

Increased exposure to sunlight (to help increase vitamin D levels) and/or vitamin D supplementation

Regular weight-bearing exercises (e.g. walking, running)

Further reading

1. Bijlsma JWJ, Hachulla E. EULAR Textbook on Rheumatic Diseases. 2nd edition, 2015. London: BMJ Publishing Group Ltd
2. Fracture Risk Assessment Tool (FRAX®). http://www.shef.ac.uk/FRAX/
3. UpToDate. https://www.uptodate.com

25.6 Rheumatoid arthritis

De nition

Rheumatoid arthritis is a chronic in ammatory disorder that typically a ects small and medium-sized joints in a symmetrical fashion

Heterogenous disease with variable mode of disease onset and disease course

Prevalence

0.5–1% of European and North American adults

Female:male ratio 3:1

Pathophysiology

Generally accepted to be an autoimmune disease despite failure to identify a dominant arthritogenic antigen

Aetiology thought to be an interplay of genetic (in particular, HLA-DRB1 alleles) and environmental factors (most importantly smoking)

Many important cell types and cytokines (T cells, B cells, mast cells, monocytes, and in ammatory cytokines), which are now therapeutic targets

Diagnosis

Clinical diagnosis based on signs and symptoms

Swelling of MCP, proximal interphalangeal, wrists, and metatarsophalangeal (MTP) joints is typical of disease at onset

ESR/CRP not always elevated

Anti-CCP antibodies (or ACPA) is found in 60–70% of RA patients and is more speci c than rheumatoid factor for the disease

US can detect synovitis and erosions in early disease

MRI can detect early erosions and bone marrow oedema (non-speci c). Synovitis can be seen with gadolinium enhancement

X-ray of hands and feet: joint space loss and erosions in established disease

Treatment of early disease

1. Early introduction of **cDMARDs** as priority (methotrexate is the anchor drug, in both monotherapy and combination therapy, due to favourable e cacy:toxicity ratio)

2. **Alternative cDMARDs** (le unomide, sulfasalazine, and hydroxychloroquine) can be used in combination with methotrexate or as an alternative to methotrexate
3. **Steroids** in low to moderate doses can be used in early disease, although long-term use should be avoided
4. Patients who do not respond to maximum-dose methotrexate, or an alternative cDMARD (sequentially or in combination), are considered for **biologic therapy (T cell co-stimulation inhibitor, TNF alpha inhibitor, B cell inhibitor, IL6 inhibitor, JAK inhibitor)**
5. Patients on biologic therapy are usually continued on methotrexate, or an alternative cDMARD
6. Flare-ups can be helped by short-term **NSAIDs or intra-articular steroid**, with upward titration of cDMARD/biologic therapy to avoid further disease are
7. **Education and emotional support** to include pregnancy and work issues
8. Access to **physiotherapists, podiatrists, and occupational therapists**

Treatment of long-standing disease

1. **Ongoing assessment** to distinguish mechanical from in ammatory problems
2. **Surgical referral** for carpal tunnel decompression, tendon repairs, and arthroplasty
3. Cervical spine assessment prior to anaesthesia because of risk of atlanto-axial subluxation
4. **Detection of systemic complications** such as vasculitis, neuropathies, secondary Sjögren's syndrome, and pulmonary brosis
5. Detection and management of **risk factors for cardiovascular disease**
6. Treatment for **osteoporosis**
7. **Adequate analgesia** (paracetamol, **NSAIDs**, occasionally opioids and anti-neuropathics)
8. Encouragement to **exercise**
9. Help with **mobility aids and home adaptations** if required
10. Occasional use of blocks (e.g. occipital nerve block, suprascapular nerve block)

Further reading

1. Bijlsma JWJ, Hachulla E. EULAR Textbook on Rheumatic Diseases. 2nd edition, 2015. London: BMJ Publishing Group Ltd

25.7 Systemic lupus erythematosus

De nition

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a broad spectrum of clinical presentation encompassing almost all organs and tissues

Incidence

20–150 per 100 000 (depending on ethnicity)

Female:male ratio 9:1

Pathophysiology

Interaction between hormonal status, genes, and environment changing immune tolerance to endogenous nuclear antigens

Diagnosis

Requires integration of symptoms, physical examination ndings, and results of diagnostic tests

65% of patients have disease onset aged between 16 and 55 years

Most common symptoms are arthralgia, constitutional symptoms, rashes, and arthritis

Clinical manifestations also include: renal disease, Raynaud's, cognitive and psychiatric symptoms, ts, vasculitis, mouth ulcers, pancreatitis, in ammatory bowel disease, lymphadenopathy, pleurisy, pericarditis, interstitial lung disease, and thrombotic disease

Patients with suspected SLE should be speci cally asked about rashes, photosensitivity, Raynaud's phenomenon, oral ulcers, arthritis, hair loss, shortness of breath, pleuritic chest pain, fever, and fatigue

Physical examination to look for rashes, alopecia, oral ulceration, lymphadenopathy, splenomegaly, pericardial or pleural e usion, and peripheral oedema. Fundoscopy to look for cotton wool spots

BP and urinalysis at every clinical encounter because of risk of occult renal involvement

Haematological ndings include anaemia, leucopenia, or thrombocytopenia

ANA is 95% sensitive but has a low speci city

70% of patients have antibodies to dsDNA, with 95% speci city

Anti-Sm antibody in 10–30%

Patients may have positive anti-phospholipid antibodies, anti-Ro, anti-La, and anti-ribonucleoprotein (RNP)

Complement (C3 and C4) can be reduced in active disease

Further investigations: neuropsychiatric symptoms (MRI, EEG, NCS), cardiorespiratory symptoms (ECG, CXR, cardiac echocardiography, high-resolution CT chest), musculoskeletal symptoms (X-ray, US, MRI, CK, EMG), suspected renal involvement (renal biopsy), GI (amylase, CT)

Treatment

1. **Hydroxychloroquine**, alone for mild joint and skin disease, and in combination with other medications for more severe disease
2. **Corticosteroid** (high dose for severe disease)
3. **Azathioprine, ciclosporin A, methotrexate, mycophenolate mofetil, cyclophosphamide**, depending on organ involvement and severity
4. **B cell-targeted therapies** (rituximab and belimumab for refractory disease)
5. Detection and management of **risk factors** for cardiovascular disease
6. **Prevention of steroid-induced osteoporosis**
7. **Detailed advice** on fertility, pregnancy, and breastfeeding
8. **Simple analgesics/NSAIDs** if required to manage joint pain
9. Advice on **pacing and graded exercise** to help with fatigue

Further reading

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CHAPTER 26

Visceral Pain Conditions

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26.1 Overview of visceral pain

Introduction—classi cation of visceral pain

True visceral pain (tissue insult): nociception arising from neural sources in deep organs of the body

Visceral hyperalgesia (visceral allodynia): stimuli which are not noxious are interpreted as pain due to alterations in nerves carrying sensations from the viscera, causing changes in visceral sensitivity at either the peripheral or the central level

Referred pain:

- Viscero-visceral referral: one sensitized organ causes sensitization of another visceral organ
- Viscero-somatic referral: visceral pain causes referred somatic pain
- Somatic-visceral referral: somatic pain causes referred visceral pain

Overview

Common and high prevalence, e.g. renal colic, dysmenorrhoea, IBS, MI

Pain arising from internal organs of the body, including cardiac, airway structures, GI tract, and upper abdominal, renal, and reproductive organs

Prompt assessment is important as can be part of a life-threatening presentation such as MI, acute pancreatitis, bowel obstruction, and peritonitis. Due to its di use nature, poor localization, and changing nature over time, it is di cult to distinguish life-threatening from non-life-threatening visceral pain syndromes such as IBS

Concurrence of visceral and somatic pain syndromes is common

Multiple factors cause and/or modify visceral pain such as psychosocial stress, mental health disorders, genetic factors, life events (e.g. abuse, life-threatening event, trauma), and biomedical factors

True visceral pain/visceral nociception

Vague, di use, poorly de ned sensation felt in the midline, regardless of the internal organ of origin

There are various causes such as infection, in ammation, mechanical stretch/distension/obstruction, neoplasm, ischaemia, e.g. myocardial ischaemia, and renal stones

Pain from the pancreas, gall bladder, duodenum, heart, stomach, and oesophagus is normally felt in the upper abdomen and lower sternum. Palpation in this area does not normally worsen the pain

Can be described as a compression or pressure

Poor correlation between the intensity of pain and the magnitude of internal organ damage, e.g. patients with angina can have severe pain, compared with silent MI which is painless

Can be associated with strong emotional (anxiety, fear, angry) and autonomic (pallor, sweating, discomfort, nausea, vomiting, bradycardia, low BP, diarrhoea) responses

Visceral hyperalgesia/visceral allodynia

Slow and poorly localized, and may not even feel like pain, e.g. colic, abdominal distension/bloating

Pain from normal physiological visceral stimulus due to increased sensitivity of that organ when there is no tissue insult, e.g. eating food in functional dyspepsia or passing urine in painful bladder syndrome

Visceral hyperalgesia can be associated with a nociceptive, neuropathic and/or an in ammatory process

It can also be associated with a traumatic event such as abuse, maternal separation, war, and torture

Some causes of visceral hyperalgesia:

- Thorax: non-cardiac chest pain, functional dyspepsia
- Abdomen: idiopathic dyspepsia, IBS, functional abdominal pain
- Pelvis: painful bladder syndrome, urethral pain syndrome, persistent interstitial cystitis, chronic non-bacterial prostatitis, pudendal neuralgia, vaginal pain syndrome, vulvar pain syndrome, anorectal pain syndrome

Viscero-visceral referral

One sensitized organ causes sensitization of another organ when the two internal organs share a common sensory a erent nerve or from a erent 'cross-talk' in the DH

Some causes of viscero-visceral referral:

- The heart and gall bladder have overlapping (T5) a erent pathways: in patients with IHD and gall bladder disease, treatment of gall bladder calculi can reduce the number of angina attacks and coronary revascularization can reduce the number of biliary colics
- The renal system and the uterus have overlapping a erent nerve pathways (T10–L1 a erents)—patients treated with hormonal therapy for dysmenorrhoea can decrease the frequency of renal colics

Viscero-somatic referral

Visceral pain causes referred somatic pain. Thorough history, examination, and investigations must be done to determine if pain is somatic or referred

Somatic referred pain is better localized, sharper, and less likely to be associated with emotional and neurovegetative signs. It can have a similar presentation to deep somatic nociceptive pain

Somatic referred pain can be associated with hyperalgesia, resulting in increased sensitivity in muscles, skin, and SC tissue innervated by the somatic spinal nerve. For example, patients with dysmenorrhoea can have tenderness on deep palpation of the suprapubic area between painful periods

Example of pain syndromes with viscero-somatic referral:

- Renal colic: hypersensitive lumbar muscles (quadratus lumborum, obliques) and pain in ank and groin, even after the calculi have been passed
- Acute myocardial ischaemia: pain in the chest radiating down the arm (C8–T1 dermatomes)

Somatic-viscero referral

Similar mechanisms to those of viscero-somatic referral

Deep palpation of muscle can reproduce visceral pain in people with profound muscle hyperalgesia. For example, deep palpation in ank and groin can elicit visceral pain from the genitourinary system even after a renal calculi has been passed

Treatment of somatic referred pain can improve visceral pain.

Management

Good patient/doctor relationship

Address the underlying pathology

Ensure that there are no red ags/pathologies amenable to treatment. Sometimes the cause of the pain is not identi ed

Patient education, realistic goal setting, healthy lifestyle, and weight control

Multidisciplinary and multimodal approaches

Important to address the psychosocial components of the presentations

Psychology: CBT, hypnotherapy, ACT, or other psychological treatments

Physiotherapy: pacing, regular exercise/stretching, or other treatments that improve function and prevent deconditioning

Interventional pain medicine can be highly e ective in some visceral presentations:

- SCS can be e ective in selective patients with chest pain from angina (improved myocardial oxygen delivery and reduction of frequency of angina attacks), IBS (sacral SCS), functional dyspepsia (may work by improving gastroparesis), and refractory pelvic pain
- Neurolytic blocks are highly e ective for cancer pain, e.g. coeliac block in pain from pancreatic cancer (its use in pain from chronic pancreatitis is controversial)

Pharmacotherapy:

- Anti-neuropathic agents: TCAs, SNRIs, gabapentinoids (more information on antidepressants and gabapentinoids can be found in Chapters 9 and 10)
- Spasmolytics: antispastics (e.g., baclofen), benzodiazepines (e.g., diazepam, clonazepam, temazepam), non-benzodiazepine antispasmodics (carisoprodol, cyclobenzaprine, metaxalone, methocarbamol, thiocolchicoside, tizanidine, tolperisone, orphenadrine) and miscellaneous (botulinum toxin, eszopiclone). The choice of muscle relaxant and evidence supporting di erent muscle relaxants is very variable and long-term use of some of these medications are associated with patient harm. Some of these spasmolytics are discussed in more detail in Chapter 13 (13.1 baclofen, 13.3 botulinum toxin, 13.7 clonazepam, 13.15 orphenadrine)
- Anxiolytics: atypical antipsychotics such as quetiapine, -2 agonists, antidepressants, BZDs in highly selected patient groups in the short term
- Avoid reliance on opioids

Visceral pain in the elderly

Visceral pain is more common in the elderly

Visceral pathologies have more atypical presentations in the elderly:

- Cardiovascular—some studies quote up to 30% of MIs in the elderly are silent MIs
- Respiratory—pneumothorax
- Abdominal complaints—up to 45% of the elderly with appendicitis do not have right lower quadrant abdominal pain

Visceral pain and gender

Gender-speci c conditions: menstrual pain, labour pain, post-partum visceral pain

Anatomical di erences in di erent genders: women are more likely to develop genitourinary tract infections due to having a shorter urethra

Some conditions are more common in one gender, with no clear organic explanation, likely due to genetic factors. For example:

- Females—higher prevalence of IBS and gall bladder disease
- Males—higher prevalence of IHD

Further reading

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26.2 Chronic abdominal pain

De nition

Chronic abdominal pain is continuous or intermittent abdominal pain or discomfort lasting for at least 6 months

Incidence

The incidence of chronic abdominal pain and the aetiology in paediatric, adolescent, and adult populations vary and treatment modalities di er

The aetiology is multifactorial and variable in each age group

Unspeci ed abdominal pain is reported in 22.9 per 1000 person-years

Epidemiological studies describe 25% of the population reporting abdominal pain

Di erences in reporting, depending on ethnicity and geographical regions

Anatomical correlation

Pain may arise from any structures inside the abdomen, or it could be referred pain

It may originate from visceral organs, MSK parts, or neural tissue

Common causes

Broadly classi ed as:

- Gastrointestinal
- Genitourinary

Gynaecological
Neurological
Metabolic
Psychological
Functional

Pathophysiology

Induced by stimulation of visceral nociceptors
This can lead to both peripheral and central sensitization, which explains the ampli cation of pain perception and referred pain to other parts of the body
The interaction between visceral pathology and altered central pain processing causes discrepancy between objective signs peripherally and increased central pain perception
Central sensitization and psychological causes have a poor prognostic outcome

Common underlying pathologies

In ammatory causes

In ammatory bowel disease
Chronic pancreatitis
Chronic appendicitis
Coeliac disease
Pelvic in ammatory disease
Primary sclerosing cholangitis
Fibrosing mesenteritis
Eosinophilic gastroenteritis

Infection

Parasites
TB
Viral infections
Other bacterial infections (*Helicobacter pylori*)

Vascular

Mesenteric ischaemia
Coeliac artery syndrome
Superior mesenteric artery syndrome

Metabolic

Diabetic neuropathy
Hereditary angio-oedema
Familial Mediterranean fever
Porphyria

Neuromuscular causes

Anterior cutaneous entrapment syndrome
Myofascial pain syndromes, e.g. rectus abdominis syndrome
Twelfth rib syndrome
Thoracic neuropathy

Radiculopathy secondary to back problems
Hernias
Levator ani syndrome

Functional

Constipation
IBS
Sphincter of Oddi dysfunction
Functional abdominal pain syndrome
Dyspepsia
Gastroparesis

Other

Peptic ulcer
Gallstones
Endometriosis
Adhesions
Neoplasms
Intestinal obstruction
Lactose intolerance
Food allergies
Intestinal malrotation

Diagnosis

History

Detailed history is paramount, including history of origin, duration, character, radiation, relationship to food, medications (opioid-induced constipation and OIH), changes with body position, previous abdominopelvic surgeries, and positioning, especially prolonged lithotomy positioning if pelvic pain is present with abdominal pain
Type of pain—visceral, somatic, or referred
In chronic abdominal pain associated with pelvic pain ± depression, detailed psychosocial and sexual history is mandatory
Menstrual and obstetric history for females
History suggestive of any red and yellow flags

Examination/tests

General examination (a quadrant-based examination will help to identify potential pain generators, followed by inspection, palpation, percussion, and auscultation)
Manual examination of the abdomen, including per vaginal and per rectal examination
Routine blood tests—FBC, LFTs, amylase, lipase, Hb electrophoresis, porphyrin levels, lead, inflammatory markers (CRP, ESR)
Stool examination—parasites, occult blood
Urine examination—infection
Endoscopy—gastroscopy, colonoscopy, cystoscopy, sigmoidoscopy
Barium studies
Laparoscopic examination
USS/MRI/CT—mainly to rule out sinister pathologies

Di erential diagnosis

Di erential diagnosis is di cult as multifactorial aetiology in chronic abdominal pain. Depending on the clinical picture, a possible di erential diagnosis is made based on the primary organ involved and neighbouring structures

Treatment

A multidisciplinary and multimodal approach is crucial for success of therapy as for other chronic pain conditions

Conservative (some with limited evidence)

Lifestyle change—to avoid constipation and food if intolerance, weight reduction, to stop smoking, and to avoid excessive alcohol consumption
Adapting sitting position
Physiotherapy for MSK structures
Acupuncture
Heat/cold application
TENS
CBT and other psychotherapies
Biofeedback techniques
Nutritional therapy

Pharmacological

Simple analgesics
Anti-neuropathic medications—anticonvulsants, antidepressants
Avoid chronic use of opioids as can cause constipation and OIH
Proton pump inhibitors if indicated
Treat infections
Nutritional supplements

Interventions (under X-ray, CT, or US guidance as indicated)

Nerve blocks—peripheral, DRG, nerve root block, and neuraxial block
LA and steroid injection (TPIs or facial plane blocks)
Epidural—thoracic/lumbar/caudal
Sympathetic block—coeliac ganglion, aorto-renal ganglion, superior mesenteric ganglion, mesenteric ganglion, and hypogastric plexus

Neuromodulation techniques

RF denervation or pulsed RF of DRG, nerve roots, peripheral nerves, or sympathetic chain
SCS/DRG stimulator or peripheral nerve stimulator—only in selected cases (currently limited evidence as it is an emerging treatment option—many are case series)

Further reading

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26.3 Chronic pancreatitis

De nition

Chronic pancreatitis is de ned as progressive in ammatory response of the pancreas, leading to irreversible morphological changes of the parenchyma

It is characterized by mononuclear in ltration and brosis

Incidence

More common in men (3:1)

Black population has 2–3 times increased incidence

Developed world: 10/100 000; tropical countries: 20–125/100 000

50% mortality within 20–25 years of diagnosis

33-fold increase in pancreatic cancer

Anatomical correlation

Pain may arise from any structures inside the abdomen or it could be referred pain

It could originate from visceral organs or MSK parts, or it could be neuropathic pain

Aetiology

Alcohol

Smoking

Genetic/hereditary

Obstructive anomalies

Autoimmune

Metabolic

Idiopathic

Pathophysiology of chronic pancreatic pain

There are di erent mechanisms:

- Neuropathic pain
- Nociceptive pain
- Neurogenic in ammation

There is also a central sensitization process which contributes to hyperalgesia that is common in chronic pancreatitis

Diagnosis

Early diagnosis is di cult due to lack of sensitive imaging or functional markers

Clinical diagnosis is made based on:

History—pain could be intermittent. Normally in epigastric region radiating to the back. History of diarrhoea and steatorrhoea

Examination—no speci c examination ndings. Pain area can be con rmed and might reveal a pseudocyst

Presence of risk factors

Pancreatic function test—limited use

Imaging—CT/MRI/US

Endoscopy

Di erential diagnosis

Pain originating from the pancreas or neighbouring structures such as the stomach, spleen, gall bladder (e.g. stones), and IBS

Treatment

A multidisciplinary and multimodal approach is crucial for success of therapy as for other chronic pain conditions

Conservative (some with limited evidence)

Lifestyle change—stopping smoking and alcohol consumption

Nutritional therapy

Pharmacological

Simple analgesics

Anti-neuropathic medications: antidepressants (e.g. TCAs, SNRIs), antiepileptics

Avoid chronic use of opioids as this will cause increased pressure at the sphincter of Oddi and can cause deterioration of pain. It can also cause OIH

Pancreatic enzyme replacement therapy

Antioxidant therapy

Interventions

Sympathetic block: splanchnic plexus block/coeliac plexus block, followed by PRF/RF/chemical neurolysis—CT-, US-, endoscopy-, or X-ray-guided

SCS (limited evidence)

Neuromodulation techniques

RF denervation or pulsed RF of DRG, nerve roots, peripheral nerves, or sympathetic chain

Spinal cord stimulator/DRG stimulator or peripheral nerve stimulator—only in very selected cases (currently limited evidence as it is an emerging treatment option—many are case series)

Surgical

Endoscopy

Pseudocyst removal

Pancreatectomy with auto-transplant

Further reading

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26.4 Chronic pelvic pain

De nition

Pelvic pain is abdominal pain located below the level of the umbilicus, including frequently lower back pain with or without radiation into the thighs

Such pain may be acute, chronic, or intermittent and may be simulated by GI disease, such as diverticulitis, or by lumbo-sacral arthritis

In females: chronic pelvic pain can be de ned as intermittent or constant pain in the lower abdomen or pelvis of a woman of at least 6 months' duration, not occurring exclusively with menstruation or intercourse and not associated with pregnancy

Incidence

More prevalent in females: 14–40% in the reproductive age group

Prevalence comparable to that of asthma and low back pain

20–70% have improper/wrong diagnosis

Time period from presentation to diagnosis varies between 6.7 ± 6.2 years

Anatomical correlation of pain generators

Most of the time, there can be one or more anatomical structures as pain generators

Female pelvic pain

Urethra

Bladder

Vulva

Vagina

Uterus

Ovaries

Pelvic oor

Peritoneum/endometriosis

Bowel

Post-surgical/neuropathic

MSK
Psychosocial

Male pelvic pain

Urethra
Bladder
Penis
Scrotum
Prostate
Pelvic floor
Peritoneum
Bowel
Post-surgical/neuropathic
MSK
Systemic
Psychosocial

Causes

Gynaecological conditions

Endometriosis
Adhesions
Chronic pelvic inflammatory disease
Pelvic congestion syndrome
Ovarian remnant syndrome
Recurrent haemorrhagic ovarian cysts
Myomata uteri (degenerating)
Adenomyosis
Uterine retroversion
Pelvic floor and hip muscle pain
Visceral hyperalgesia
Neoplasms

Urological conditions

Urinary retention
Urethral syndrome
Interstitial cystitis
Pyelonephritis
Neoplasms

Abdominal conditions

Neuropathies
Porphyrias
IBS
Bowel obstruction
Diverticulitis
Hernia
Neoplasms

Neurological conditions

Nerve entrapment syndromes
Generalized myofascial pain syndrome
Fibromyalgia

Musculoskeletal conditions

SIJ pain
Hip pain
Pubic dysfunction
Spine pathology

Psychological conditions

Depression
PTSD (history of abuse/trauma)
Anxiety disorders
Personality disorder

Diagnosis

History—a detailed history is paramount. Take a detailed history of origin, duration, character, radiation, previous abdominopelvic surgeries, and positioning during surgery, especially prolonged lithotomy positioning
In chronic pelvic pain associated with depression, a detailed psychosocial and sexual history is mandatory
Menstrual and obstetric history for females
History suggestive of any red and yellow flags
General examination
Manual examination, including vaginal and rectal examination
Laparoscopic examination
USS/MRI/CT—mainly to rule out sinister pathologies
Colonoscopy, cystoscopy, and sigmoidoscopy

Differential diagnosis

Differential diagnosis is very difficult as multifactorial causes found in chronic pelvic pain
Depending upon the clinical picture, a possible differential diagnosis is made, based on the primary organ involved and neighbouring structures

Treatments

A multidisciplinary and multimodal approach is crucial for success of therapy as for other chronic pain conditions

Conservative (some with limited evidence)

Lifestyle changes
Adapting sitting position
Coccyx cushion if appropriate
Physiotherapy for pelvic floor structures and manipulation
Therapeutic US therapy
Acupuncture

Heat/cold application
TENS
CBT, other psychotherapies
Biofeedback techniques
Nutritional therapy

Pharmacological

Simple analgesics, especially NSAIDs if there is no contraindication
Anti-neuropathic medications—TCAs (e.g. amitriptyline), anticonvulsants (e.g. pregabalin, gabapentin), SNRIs (e.g. duloxetine)
Opioids—may be used only for acute are-ups. Opioids used as long-term treatment is associated with worse outcome

Interventions

LA and steroid injection under X-ray or US guidance (60–85% success rate)
Caudal block
Ganglion impar block
Sacral nerve root block
RF denervation or pulsed RF of nerve roots

Neuromodulation techniques—only in selected cases

(Currently limited evidence as it is an emerging treatment option—mostly case series)

TENS
Peripheral eld stimulation
PNS, depending on pathology
Pudendal nerve stimulation
Sacral stimulation
DRG stimulation
SCS

Surgical

Depending on the cause of pelvic pain, appropriate surgery may be indicated

Additional information

Most of the time, chronic pelvic pain is associated with chronic abdominal pain and presents as chronic abdominopelvic pain
Treatment depends upon the pain generator and also the pathophysiology
There may be a need to treat both conditions together (see 26.2 Chronic abdominal pain, p. 530)

Further reading

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26.5 Vulvodynia

De nition

The International Society for the Study of Vulvovaginal Disease (ISSVD) de nition of vulvodynia is vulvar pain of at least 3 months' duration without a clear identi able cause which may have potential associated factors

It is a diagnosis of exclusion and is an idiopathic pain disorder

Incidence

3–7% of reproductive age group

Only 1.4% of women seeking medical advice are correctly diagnosed

Aetiology

Cause is unknown

Contributing factors

Neuropathy (increased nerve bres in the region or spinal nerve injury)

Chronic vaginal dryness

Sjögren's syndrome

Genetic predisposition to in ammation

Allergy or sensitivities

Pelvic oor dysfunction

Anatomical correlation and pathophysiology

It is very complex due to variation in the innervation

The vulva is innervated by:

- Anterior labial branch of the IIN
- GFN
- Branches of pudendal nerve

Pelvic oor muscles are divided into three groups:

- Super cial (urogenital diaphragm)
- Middle
- Deep pelvic oor muscles (anal triangle muscles and associated pelvic and hip muscles)

The pudendal artery, vein, and nerve passing through Alcock's canal provide neurovascular function of the pelvic oor

Classi cation

Generalized or localized

Primary or secondary

Provoked or unprovoked
Intermittent, persistent or constant
Immediate or delayed

Di erential diagnoses to rule out

Infection

Candidiasis
Trichomoniasis
Herpes
Human papillomavirus

In ammation

Lichen planus
Lichen sclerosus
Lichen simplex
Contact dermatitis

Neurologic disorders

Pudendal nerve, IIN, or GFN injury, entrapment, or neuropathy
Tarlov cysts

Trauma

Straddle injury
Female genital mutilation
Accidents
Sexual abuse

Neoplastic conditions

Squamous cell carcinoma

Oestrogen de ciencies

latrogenic

Persistent post-surgical pain
Nerve injury
Surgical positioning: lithotomy, laparoscopic trocar injury

History and physical examination

Detailed pain history, including psychosocial and sexual history, should be taken
Complete gynaecological examination, including external genitalia, per vaginal, and per rectal examination

Examination

Cotton sensory test
Neurosensory check—cotton vs pin prick
Pelvic oor muscle examination

Pain comorbidities

Interstitial cystitis
Endometriosis
Chronic headache
Hypermobility syndrome
Temporomandibular dysfunction

Contributing factors

Emotional well-being
Sleep interference
Relationship problems
Physical functioning
Sexual functioning

Treatment

A multidisciplinary and multimodal approach is crucial for success of therapy as for other chronic pain conditions

Conservative/self-management

Exercise and physical therapy—pelvic oor muscle exercises, yoga, massage, soft tissue work, dilators, and biofeedback
Healthy diet—especially low-oxalate diet
Stress management
Psychotherapy, including mindfulness and CBT
Sexual therapy
Acupuncture

Medications

Simple analgesics
TCAs—commonly amitriptyline and nortriptyline
SNRIs—commonly duloxetine and venlafaxine
Anticonvulsants—commonly gabapentin, pregabalin, topiramate, lamotrigine, and carbamazepine
Topical—antifungal, corticosteroids, lidocaine, oestrogen, testosterone, ketamine, and gabapentin

Interventions

Mainly targeting nerves supplying the vulvar region
Nerve blocks—GFN, IIN, or pudendal nerve block
Pulsed RF of nerves
Neuromodulation:
- TENS
- Peripheral nerve neuromodulation
- SCS

Surgery

Reserved for provoked vestibular vulvodynia

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26.6 Refractory angina pectoris

De nition

Severe chest pain, heavy retrosternal pain, referred pain (arm, neck, jaw)

It is refractory if conservative treatments fail

Pathophysiology

Due to coronary obstruction or spasms (insu cient blood and oxygen supply to the heart, increased oxygen consumption)

Risk factors

Smoking, obesity, hypertension, diabetes, high cholesterol

Diagnosis

History

Retrosternal pain often radiating to the arms, neck, throat, jaw and teeth (especially on the left side)

Sweating, nausea, vomiting

Symptoms provoked by exertion and disappear at rest

Triggered by emotional stress, exposure to cold, meals, and smoking

Refractory if repeated reversible myocardial ischaemia occurs despite optimal treatment with severe coronary stenosis (>75%)

Examination/tests

Cardiological workup needed

12-lead ECG at rest or exercise stress test on ergometer (ischaemic signs)

Stress echocardiography

Angiography, CT angiography

Di erential diagnosis

Respiratory (pulmonary hypertension, pulmonary embolism, pleuritis, pneumothorax, pneumonia)
Cardiac valve disease (mitral prolapse, cardiac syndrome X)
GI: peptic ulcer, pancreatitis, oesophageal spasms, re ux, cholecystitis
MSK: costochondritis, Tietze's syndrome, thoracic trauma, cervical arthritis, myositis, cancer
Spinal cord injury, thoracic radiculopathy
Aortic dissection, post-herpetic neuralgia, panic disorder

Treatment

Conservative (under cardiology)

Reduce oxygen demand (-blockers, Ca^{2+} channel blocker)
Increase oxygen supply (nitrates, angioplasty, coronary artery bypass grafting (CABG))
Anti-cholesterol and antiplatelet drugs
Good progress has been made with anti-cholesterol and anti-anginal drugs, and better quality of percutaneous angioplasty

Spinal cord stimulator

Patients with substantial limitation due to angina despite all conservative and surgical therapies (must have been investigated by a cardiologist)
Indications are controversial
Evidence: 2B+ (recommended in specialized centres)
E ects:
- Less pain (GABA, dopamine, glycine)
- Anti-anginal (normalization of the cardiac nerve system)
- Less medication use, higher exercise tolerance
- Anti-ischaemic e ects, fewer attacks (increased angina pectoris threshold, redistribution of coronary blood ow?)
- Angiogenesis (collaterals)
- SCS does not mask acute myocardial infarcts

E cacy:
- Better exercise tolerance, improved QoL after 12 months
- Improved symptoms after 12 months
- Reduced mortality, reduced cerebrovascular accidents (versus CABG patients)
- SCS may be an alternative to surgery in selected patients

Complications:
- Lead migration, electrode fracture (7%)
- Battery failure, SC infection
- No major complications described

Absolute contraindications:
- De brillating pacemaker
- Bleeding diathesis
- Neuraxial malignancies
- Severe cognitive disorders

Technique:
- Asepsis, prophylactic antibiotics
- Tuohy needle insertion at T8/T9

Electrode tip at T2/T3 (four or eight contacts)
Mapping of painful area
Stimulator (implantable pulse generator) in buttock or upper abdomen

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CHAPTER 27

Widespread Chronic Pain

Enrique Collantes, No I Mulla, and Kavita Poply

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27.1 Chronic fatigue syndrome

Introduction

Chronic fatigue syndrome, or myalgic encephalitis or systemic exertion intolerance disease, is characterized by a wide range of symptoms, the most common being extreme fatigue

More common in women and between second and fourth decades

Pathophysiology

Pathophysiology is not well understood and some of the mechanisms involved include:

Altered pain processing—descending inhibitory serotonergic pathways

Genetic factors—familial, methylenetetrahydrofolate reductase gene

Infections—many patients describe the onset after an infection:

- Viral infections such as Epstein–Barr virus, retroviruses, enteroviruses, and others
- Bacterial infections such as pneumonia

Immune system changes—higher levels of cytokines and active $CD8^+$ T cells

Endocrine–metabolic imbalance—hypometabolic state, high levels of insulin-like growth factor, low cortisol, low corticotropic hormone secretion, abnormalities in metabolism of lipids, amino acids, and sugars to make energy

Mental health problems—depression, PTSD

Sleep disorders

Environmental stressors

Psychosocial contributors

Investigations

Investigations are not needed for diagnosis

Investigations are performed to exclude other causes such as FBC, in ammatory markers (CRP, ESR), CK, thyroid studies, and other tests assessing for other causes

Diagnostic criteria

Chronic fatigue lasting >6 months

Plus at least one of the following clinical features of moderate to high severity at least half of the time: post-exertional malaise (>24 hours), subjective memory impairment, tender lymph nodes, MSK pain, headache, unrefreshing sleep, and orthostatic-related symptoms

Major interference with productivity, leisure, rest, and daily activities

Di erential diagnosis

Fibromyalgia

Somatoform disorder, conversion disorder, illness anxiety disorder

Hypothyroidism/hyperparathyroidism

Autoimmune disorders—RA, SLE, Sjögren's syndrome, polymyalgia rheumatica, myositis

HIV, Lyme disease, hepatitis C

Drug-related—statins, aromatase inhibitors, bisphosphonates

Sleep apnoea

Malignancy—multiple myeloma, metastatic cancer

Treatments

Validate, use an empathic approach, and develop trust with the patient

Patient education on chronic fatigue syndrome:

- It is not life-threatening but can cause signi cant disability
- The cause is not completely understood, but multiple mechanisms are involved—genetic, endocrinological, neurological, metabolic, immunological, environmental, psychosocial, and mental health factors
- Address the patient's concerns, beliefs, and expectations
- Treatment focuses on reducing symptoms, impairment, and disability

Treating modi able perpetuating factors—depression, cognitive impairment, sleep, unhelpful thoughts/behaviours, disconnection from the community

Healthy lifestyle (weight control, balanced diet, improving general tness, not smoking or drinking alcohol, exercise)

CBT

Graded exercise therapies with pacing

Short drug trials addressing speci c presentations—pain, mood, anxiety, etc.

Workplace and non-work-related ergonomic changes

Additional information

Conditions that can coexist:

- Regional pain syndromes: IBS, temporomandibular joint dysfunction, tension headaches, idiopathic low back pain, vulvodynia
- Depression, panic attacks, generalized anxiety disorder, PTSD

Further reading

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3. Meeus M, Nijs J, Meirleir KD. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. Eur J Pain 2007;11(4):377–86

27.2 Fibromyalgia

Introduction

Widespread chronic pain syndrome, with a prevalence of 2% in the general population

Heterogenous condition a ecting all four quadrants of body. It presents with pain being a dominant symptom, but it can also be associated with fatigue, mood swings, and cognitive impairment as part of a spectrum

Pathophysiology

There are several proposed mechanisms, but no clear pathophysiological mechanism exists:

- CNS pain processing abnormalities resulting in hyperexcitability of pain-transmitting neurons
- Dysfunction of descending inhibitory pathways
- Abnormal function of HPA axis
- Disturbances in the balance between serotonergic and dopaminergic mechanisms
- Strong familial component— rst-degree relatives of patients with bromyalgia are 8.5 times more likely to have the disorder than the general population

Investigations

Not needed for diagnosing bromyalgia

Investigations are performed to exclude other causes. Investigations routinely performed include FBC, in ammatory markers (CRP, ESR), CK, thyroid studies, and other tests assessing for other causes

Di erential diagnosis

Chronic fatigue syndrome

Somatoform disorder, conversion disorder, illness anxiety disorder

Hypothyroidism/hyperparathyroidism

Autoimmune disorders—RA, SLE, Sjögren's syndrome, polymyalgia rheumatica, myositis

HIV, Lyme disease, hepatitis C

Drug-related—statins, aromatase inhibitors, bisphosphonates

Sleep apnoea

Malignancy—multiple myeloma, metastatic cancer

Diagnosis—American College of Rheumatology diagnostic criteria

1990 diagnostic criteria: traditionally diagnosed as speci c tender points on palpation (>11/18)

2010 diagnostic criteria: physician-based criteria valid for individual patient diagnosis. It accounted for both peripheral and somatic symptoms, simplifying the diagnosis of bromyalgia. Suitable for use in primary care without requiring a tender point examination

2011 diagnostic criteria: revised criteria more patient-reported and suitable for research purposes. It led to misclassi cation when applied to regional pain syndromes

Median sensitivity and speci city of the 2010 and 2011 criteria were 86% and 90%, respectively, providing an improved diagnostic accuracy to the previous 1990 criteria

Table 27.2.1 American College of Rheumatology 2016 diagnostic criteria for bromyalgia

1. Generalized pain, de ned as pain in at least four of ve regions (axial plus upper and lower segments plus left- and right-sided pain), is present
2. Symptoms have been present at a similar level for at least 3 months
3. Widespread pain index (WPI) 7 and symptom severity scale (SSS) score 5 or WPI of 4–6 and SSS score 9
4. A diagnosis of bromyalgia is valid, irrespective of other diagnoses. A diagnosis of bromyalgia does not exclude the presence of other clinically important illnesses. Now a more recent 2016 revision has been proposed adding a widespread pain criterion

WPI:
Note the number of areas in which the patient has had pain over the past week (score will be between 0 and 19): left shoulder girdle, right shoulder girdle, left hip (buttock, trochanter), right hip (buttock, trochanter), left jaw, right jaw, upper back, lower back, left upper arm, right upper are, left lower arm, right lower arm, left upper leg, right upper leg, left lower leg, right lower leg, neck, chest, abdomen

SSS score:
A. Fatigue, waking unrefreshed, cognitive symptoms. For each of these three symptoms, indicate the severity over the past week, using the following scale:
   a. Score 0: no problem
   b. Score 1: generally mild or intermittent
   c. Score 2: often present at a moderate level
   d. Score 3: severe, pervasive, continuous, life-disturbing problems
B. Somatic symptoms: indicate whether the patient has 0, no symptoms; 1, few symptoms; 2, a moderate number of symptoms; or 3, many symptoms. Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhoea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing di culties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms

   The SSS score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent of the somatic symptoms in general. The nal SSS score is between 0 and 12

Reproduced from Wolfe, F., et al. (2010). The American College of Rheumatology Preliminimary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthiritis Care and Research*. 62(5): 600–610. DOI 10.1002/acr.20140.

2016 diagnostic criteria: provides a better diagnostic accuracy by combining physician and questionnaire criteria, minimizing misclassi cation of regional pain disorders, and eliminating the previously confusing recommendation regarding diagnostic exclusions (see Table 27.2.1)

Management

Early diagnosis and patient education form the key components of a multidisciplinary management approach recommended by the European League against Rheumatism (EULAR) At the outset, patients need to be o ered individual graded exercise therapy that can be combined with non-pharmacological. If symptoms are predominantly associated with depression, anxiety, and poor coping skills, psychological therapies such as CBT should be considered. On the other hand, pharmacotherapy may be helpful in managing the pain component with sleep disturbance and anxiety

Non-pharmacological management

Should be considered as the rst step in the management of bromyalgia—a key component of multimodal pain management, avoiding pharmacological-related S/Es:

Exercise: strongly recommended early in treatment pathway. Both aerobic and strengthening exercise programmes are recommended

CBT: e ective at producing modest long-term reductions in pain and disability, and improving mood

Acupuncture: can be o ered early in management as added to standard therapy—resulted in 30% (21%, 39%) improvement in pain and fatigue

Mindfulness/mind–body therapy: results in short-term improvements in pain and QoL

Meditative movement therapies: t'ai chi, yoga, qigong, or body awareness therapy have demonstrated improvements in sleep, fatigue, and QoL. Regular use of these therapies may result in improvement, some of which is maintained longer term

Pharmacological management

Should be considered in relation to individual symptoms in association with pain such as fatigue and disability

Amitriptyline (TCA):

30% pain reduction, risk reduction (RR) 1.60, 95% CI 1.15–2.24

NNT 3.54, 95% CI 2.74–5.01

Moderate e ect on sleep and fatigue

25 mg daily has been shown to improve pain intensity, with no additional bene t demonstrated at 50 mg dose

Pregabalin (gabapentinoids):

75–300 mg twice daily

NNT 9, 95% CI 7–13

RR 1.37, 95% CI 1.22–1.53

Very small e ect on fatigue and sleep. Minimal e ect on disability. Evidence on gabapentin is limited to a single moderate-quality study, with, however, a signi cant e ect of 30% pain reduction (RR 1.65, 95% CI 1.10–2.48) and a similar small e ect on sleep and a larger e ect on improvement in disability

Duloxetine (SNRI):

60 mg/day has been e ective at reducing >30% pain (RR 1.38, 95% CI 1.22–1.56), with NNT 6 and 95% CI 3–12, with small e ects on sleep and disability, but no e ect on fatigue

Milnacipran has been reported to have 30% pain reduction (RR 1.38, 95% CI 1.25–1.51), a small bene t on fatigue and disability, and no e ect on sleep

Opioids, NSAIDs, and SSRIs have poor evidence. Furthermore, opioids should be avoided because of the risk of addiction, dependence, and other adverse e ects (see Chapter 7)

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CHAPTER 28

Other Pain Conditions

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28.1 Acute pain

Introduction

Acute pain is pain of recent onset and limited duration (<3 months)

Chronic pain usually persists for longer than 3 months or beyond the usual duration of an acute injury or disease

There are di erences between acute and chronic pain and require di erent approaches to treatment

Poorly controlled acute pain may contribute to the development of chronic pain which has wider rami cations for the patient and society

More attention is needed for patients who are pregnant, elderly, opioid-tolerant, or disabled (physical, cognitive, visual/hearing impairments), those with substance abuse disorder, sleep apnoea, or renal or liver disease, and those who do not speak English and from ethnic minorities

Pathophysiology

Normally nociceptive (somatic and/or visceral) and/or neuropathic

Tissue injury in the peripheral and/or central nervous system causes an in ammatory response

Peripheral and/or central sensitization can develop, which results in increased sensitivity of the somato-sensory nervous system to noxious and non-noxious stimuli. Complex interplay of mechanisms that go beyond the sensory/discriminative aspects can result in long-term reorganization of the nervous system (see Chapter 2 for further information)

Characteristics of acute pain

Short-lived

Types of pain

- Nociceptive pain (somatic pain ± visceral pain)
- Neuropathic pain

Leads to adaptive behaviours
Appropriate biological responses
Normal baseline neuronal sensitivity
Does not usually lead to disability

Advantages of e ective acute pain management

Improved patient and sta satisfaction
Improved quality of care, patient safety, and cost-e ectiveness
Earlier mobilization
Reduced patient complications
Reduced duration of stay and re-admissions to hospital for pain management problems
Less use of health care resources
Well-controlled acute pain may reduce the incidence of persistent pain

Assessment

Biopsychosocial approach
Consider if the pain is neuropathic ± nociceptive (somatic ± visceral)
Detailed pain-orientated history
Relevant medical and surgical history
Identify perpetuating factors: expectations, beliefs, mood disorders, psychosocial stressors, litigation, coping skills
Current and previous treatments
Pain assessment tools:

- For initial assessment, ongoing evaluation and response to treatments
- Unidimensional tools commonly used are the NRS, VRS, and VAS. Pain scores should never be used alone to determine pain intensity
- Functional assessment is crucial, e.g. functional activity score
- Observational pain assessment tools should be used if patients cannot respond verbally or cannot self-report
- Pain-orientated physical examination and exclude red ags

Management

General overview

Address the underlying organic cause
Address patient expectations and beliefs, and develop a good therapeutic relationship with the patient. Patients need to understand that being completely pain free is usually not achievable and the key goal of analgesia is to facilitate recovery, mobilization and physiotherapy
Patient and sta education, and multidisciplinary and multimodal approaches positively in uence outcomes
Frequent assessment and reassessment of the e ect of all interventions are essential. Slow analgesic titration and avoidance of a rapid increase in opioid analgesia or other analgesics with sedating properties is important

Unexpected onset of pain or poorly controlled pain may be from an established or new surgical, medical, and psychiatric diagnosis

Acute neuropathic pain is normally under-recognized and undertreated. Treatments which can work more quickly and may be appropriate include opioids (tramadol and tapentadol), gabapentinoids, and ketamine

Preventative analgesia—level 1 evidence for ketamine, LAs, and certain regional techniques (refer to other sections of the book)

PROSPECT (PROcedure-SPECi c post-operative pain managemenT) provides evidence-based treatments of pain for speci c operations

Multimodal pain management

Multimodal pain management combining pharmacological and non-pharmacological techniques provide more e ective analgesia reducing S/Es and adverse e ects

Non-pharmacological treatments

- Input from physiotherapy, OT, and psychology
- Pain management strategies can include activity pacing, problem-solving, attention diversion (book, music, videos, or others), thought management, goal setting, acupuncture, TENS, biofeedback, hypnosis, and relaxation/meditation techniques

Pharmacological treatment

- Multimodal Analgesia: paracetamol ± NSAIDs ± opioids ± adjuvants
- PCA is indicated in the early post-operative setting and when patients cannot have oral intake
- Due to patient factors, environmental factors, and individual opioid characteristics (e.g. in renal failure, avoiding opioids that have active metabolites, etc.), some opioids may be more appropriate in some circumstances (see Chapter 7 for further reading). Patients on sedating agents and/or opioids need to be adequately assessed and monitored for ventilatory impairment
- Adjuvants are opioid-sparing and decrease opioid-related S/Es
- Adjuvants include ketamine, lidocaine, gabapentinoids, -2 receptor agonists (clonidine, dexmedetomidine), steroids (dexamethasone), and antidepressants
- Consider drugs, such as Entonox® and methoxy urane, for analgesia during procedures

Regional analgesia and continuous peripheral nerve blocks

- Neuraxial analgesia: good evidence in abdominal and thoracic surgery
- Epidural analgesia is underutilized due to potential serious S/Es
- Continuous peripheral nerve blocks provide better analgesia than single-injection peripheral nerve blocks. Peripheral nerve blocks generally have a better safety pro le than neuroaxial blocks

Further reading

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28.2 Chronic post-surgical pain

De nition (IASP)—multiple de nitions exist

Chronic post-surgical pain is pain that develops or worsens in intensity after a surgical procedure and persisting beyond the healing process

Pain lasting for at least 3 months after surgery, signi cantly a ecting QoL

The pain can be a continuation of acute post-surgical pain or develop after an asymptomatic period (after several months or even years)

Pain is localized to the surgical eld or projected to the innervation territory of a nerve or referred to a dermatome

Other causes for pain excluded (e.g. malignancy, infection, pain from pre-existing pain problem)

It is one of the most common complications after surgery

Incidence

On average, CPSP occurs in 1–2 of ten surgical patients, but it varies with the type of surgery (see Table 28.2.1)

The incidence of severe CPSP is between 2% and 25%

2% of post-operative patients reported severe CPSP one year after surgery

Intolerable CPSP occurs in about one of every 100 operations

Neuropathic pain is present in up to 80% of patients with CPSP

Pathophysiology

Damage to major nerves during surgery (however, CPSP can develop in the absence of nerve damage)

Persistent peripheral noxious stimulation

Table 28.2.1 Incidence of chronic post-surgical pain (CPSP)

Type of surgery	Incidence of CPSP
Amputation	30–85%
Caesarean section	6–55%
Cholecystectomy	3–50%
Coronary bypass	30–50%
Craniotomy	7–30%
Dental surgery	5–13%
Hip arthroplasty	27%
Inguinal herniotomy	5–63%
Knee arthroplasty	13–44%
Melanoma resection	9%
Mastectomy	11–57%
Sternotomy	7–17%
Thoracotomy	5–65%
Vasectomy	0–37%

Enduring maladaptive neuroplastic changes at the spinal DH and/or higher CNS structures
Compromised inhibitory modulators of noxious stimulation in medullary-spinal pathways
Impaired descending facilitatory modulation
Maladaptive brain remodelling in structure, function, and connectivity

Risk factors

Demographic factors:
- Young age (but not very young age)
- Female sex
- Sociodemographic (educational, socioeconomic, compensatory, employment-related factors)

Genetic predisposition:
- Heritability of chronic pain is estimated between 30% and 70%
- Genetic variations exist in drug metabolism and neurological pain pathways
- Some genetic polymorphisms are associated with CPSP (e.g. COMT on pain inhibition or *OPRM1* encoding the mu receptor)
- Monozygous twins manifest partial concordance in the development of pain and in ammation; therefore, epigenetics may also play a role in the development of CPSP

Psychosocial factors:
- Depression, psychological vulnerability, stress, late return to work
- Anxiety, catastrophizing, fear avoidance
- Comorbid stress symptoms (e.g. sleep disturbance, PTSD)
- In children, parental catastrophizing can contribute to CPSP

Pain as risk factor:
- Strongest predictor of CPSP is poorly controlled pain with severe pain in the preoperative and post-operative period
- Severe post-operative pain could be an early manifestation of subsequent CPSP
- Acute post-operative pain and the duration of severe post-operative pain on day 1 post-surgery. For every 10% increase in time spent in severe pain, the risk of developing CPSP increased by 30%

Surgical factors:
- Surgical procedure in uences the incidence (see Table 28.2.1)
- CPSP is procedure-speci c (in uence of nerve injury, increased risk of CPSP with longer duration of surgery, more traumatic and extensive approaches, repeated revisions, and when surgical complications occur; role of nerve sparing/handling surgical techniques is inconclusive)
- Even minor procedures can lead to CPSP

Medical factors:
- CPSP risk is higher with multiple comorbidities and preoperative disability (e.g. IBS, RA, Raynaud syndrome)
- The addition of chemotherapy/radiotherapy as an additional therapeutic modality
- Preoperative opioid use. Chronic opioid users may require 3–4 times the amount of opioids, compared to opioid-naïve patients

Preventative and pre-emptive measures

Surgical:
- Modi cation of surgical technique to minimize the impact of tissue trauma and intraoperative nerve injury
- Surgery duration also plays a role, although this may be a re ection on complex pathology and related to the degree of intraoperative tissue damage

Anaesthetic:

- Regional anaesthesia has the potential to reduce the severity of acute and chronic pain after surgery
- Pre-emptive epidural analgesia has a signi cant bene t on post-operative pain

Pharmacological:

- IV lidocaine, anti-neuropathic agents, gabapentinoids, antidepressants—e cacy increases with duration of treatment
- These therapies appear promising as part of a multimodal analgesic strategy (the exact dosage and duration are yet to be determined)
- Perioperative ketamine infusion appears ine ective in reducing CPSP

Psychological:

- Psychological support (including preoperative counselling)

Treatment (physical, medical, surgical, pain interventions, alternatives)

Transitional pain services aim to prevent the transition from acute to chronic pain (concept of a fully integrated peri-operative pain service)

Preoperative:

- Risk strati cation
- Discussion with surgeon (surgical approach), and anaesthetic and analgesic planning
- Transitional pain service (for perioperative management of pain)

Intraoperative:

- Surgical technique
- Anaesthetic and analgesic technique (regional anaesthesia, multimodal analgesia)

Post-operative:

- E ective analgesia
- Early management of potentially developing chronic pain

Physical therapies:

- Massage, physiotherapy, and acupuncture

Pharmacological treatment—in neuropathic pain:

- Treatment recommendations are generally extrapolated from data for other types of chronic pain, especially in neuropathic pain:
  - Anticonvulsants, TCAs, and SNRIs for neuropathic pain (rst line)
  - Paracetamol and NSAIDs can also be used in accordance with symptom severity
  - Strong opioids should be used with caution after considering the risks and bene ts

Pain interventions:

- Consider various other interventions such as nerve blocks, nerve ablation, and neuromodulation for patients in whom pharmacological intervention has not worked

Psychological interventions:

- CBT may be useful

Further reading

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28.3 Erythromelalgia

Introduction

Rare neurovascular disorder of unknown aetiology, with an incidence rate of approximately 1 in 50 000 people per year, with a higher incidence in women

Can be inherited or acquired

Clinical features

Intermittent intense burning sensations, redness, and increased temperature in the periphery, primarily a ecting the feet, but can a ect hands

Aggravating factors

Exposure to heat

Lowering the a ected limb, i.e. feet/hands

Exercise

Pressure

Relieving factors

Cooling of the a ected limbs

Lowering the a ected limbs

Types

Various subtypes, but two main classes:

- Idiopathic
- Secondary

Pathophysiology—primary or idiopathic form

Usually early-onset type presenting in childhood

It is caused by gain in function as a result of mutations in the *SCN9A* gene, which is responsible for coding Nav 1.7 channels, mainly localized in the DRG and sympathetic ganglia

Functional characterization of mutant Na^+ channels has been done by patch clamp technique and suggests slowed deactivation and increased ring frequency following stimulation

Nav 1.8 channels, which are more resistant to inactivation following depolarization, are also present in the DRG, and gain in function or hyperexcitation is the outcome manifesting as neuropathic pain

Nav 1.8 channels are not present in the sympathetic ganglion; mutation in the *SCN9A* gene results in hypoexcitation and dysfunction of sympathetic regulation, which, in turn, results in vasomotor manifestations seen in the periphery

The mechanism is thought to be similar to diabetic neuropathy, i.e. due to microvascular derangement leading to peripheral arterio-venous shunting, causing hypoxia despite increased skin blood flow, pain, and swelling, along with increased temperature (the increased temperature, in turn, can alter Na^+ channels, resulting in a potential vicious cycle)

Secondary form

Usually secondary to thrombocytosis in myeloproliferative syndromes, as a result of altered platelet functions, which, in turn, affect the microvasculature

Erythromelalgia may present years before the onset of myeloproliferative disorders (therefore, patients with erythromelalgia should be tested regularly for any abnormality of blood cells and Hb; any such abnormality should warrant full evaluation for myeloproliferative disorders, as about 10% of cases of erythromelalgia are associated with these disorders)

Diagnosis

It is an exclusion diagnosis

Based on history and clinical examination during the symptomatic period

Skin biopsy not useful in diagnosing erythromelalgia, although it can be used to exclude other conditions

Management

The aim should be to identify the disease early to achieve the best prognosis in terms of remissions and a better QoL; as such, there is no cure for the condition

Avoiding precipitating factors

Treatment of secondary causes (e.g. myeloproliferative disorders):

- Non-pharmacological measures:
  - Cooling the affected extremities (patients may end up having frostbite after using ice too frequently)
  - CBT, pain rehabilitation programme, patient support group (Erythromelalgia Association)
- Pharmacological treatment:
  - Aspirin has been found to be very effective in treatment of pain, particularly in patients with myeloproliferative disorders
  - Lidocaine patches
  - Other anti-neuropathic agents are used when the above-mentioned non-pharmacological and topical measures have failed to treat the symptoms. The ones considered to be useful from case reports and case series include gabapentinoids, venlafaxine, and TCAs
  - Other treatments with possible beneficial effects are IV lidocaine, Na^+ channel blockers, vasodilators, and IV Ig
  - Systemic steroids may also be helpful if used at early stages before central sensitization takes place

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28.4 Headaches

Introduction

Prevalence of current headache disorder (symptomatic at least once within the year) amongst adults is estimated globally to be about 50%

Impose a signi cant burden on personal su ering, nancial cost, QoL, and employment

The long-term e ort of coping with headaches may also predispose the individual to other illnesses

Diagnosis of headache

No speci c diagnostic tests, relies on accurate history

A headache diary kept over a few weeks is helpful as the pattern of attacks is a critical pointer in the diagnosis

Conditions requiring more urgent interventions must rst be ruled out

Warning features in the history

New or unexpected headache

A thunderclap (abrupt or 'explosive' onset) headache

Headache with atypical aura (duration >1 hour or including motor weakness)

Aura occurring for the rst time in a patient during use of combined oral contraceptives

New-onset headache in a patient older than 50 years or younger than 10 years

Persistent morning headache with nausea

Progressive headache, worsening over weeks or longer

Associated with postural change

New-onset headache in a patient with a history of cancer or a history of HIV infection

Types of headache disorders

Headaches are broadly classi ed as either primary or secondary

Primary headaches are benign, recurrent headaches not caused by any underlying disease or structural problems

Secondary headaches are caused by an underlying disease process which, in some cases, may be life-threatening

Primary headaches

Encompasses 90% of headaches

Include migraines, tension-type headaches, trigeminal autonomic cephalgia (TAC), and other primary headache disorders

Improved recognition of common headache disorders and better targeting of available treatments should reduce the headache burden

Specialist advice from a neurologist or a headache specialist should be sought in refractory or complex cases

Migraines

A common disabling primary headache disorder, usually begins at puberty, and mostly a ects those aged between 35 and 45 years

2:1 times more common in women, because of hormonal in uences

Moderate or severe in intensity, unilateral and pulsating, can last from 4 to 72 hours

Associated with GI symptoms that limit activity

Dark and quiet environments are preferred during an attack

Migraines can occur with or without an aura

Auras are focal neurological symptoms that can precede or accompany a headache, usually visual (transient hemianopic disturbances or spreading scotoma) and lasting 5–60 minutes

Other reversible focal de cits include unilateral paraesthesiae of the hand, arm, or face, or dysphasia

Some patients also experience a premonitory phase (hours or days before a headache) and a headache resolution phase

Premonitory and resolution symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue, and neck sti ness or pain

Acute treatment options:

- Combination therapy with an oral triptan and an NSAID or a triptan and paracetamol
- Oral triptan, NSAID, aspirin, or paracetamol as monotherapy
- Antiemetic, even in the absence of nausea or vomiting
- If one triptan is ine ective, others may work as lack of e ectiveness is not a class e ect
- If oral therapy not e ective or not tolerated, then non-oral metoclopramide or prochlorperazine can be used, in addition to a non-oral NSAID or triptan if these have not been tried
- No ergots or opioids to be o ered

Prophylactic treatment options:

- Recommended if >4 attacks of migraine per month, headaches lasting longer than 12 hours or very disabling
- Some patients need long-term prophylaxis, but review the need at 6 months after starting prophylactic treatment
- Topiramate is a recommended rst-line option but has a teratogenic risk in women of childbearing age
- Propranolol and amitriptyline are also recommended as rst-line agents
- Do not o er gabapentin as prophylaxis
- A course of acupuncture can be considered in those patients for whom topiramate and propranolol are unsuitable or ine ective

Special considerations:

- Combined hormonal contraception should not be used if a woman has migraine with aura because of a possible increased risk of ischaemic stroke
- Migraine without aura often improves during pregnancy. Paracetamol is suggested as rst choice in pregnancy. Triptan or an NSAID can be considered after weighing the risk–bene t ratio for use in pregnancy. If prophylaxis is necessary during pregnancy, discussion with, or referral to, a specialist is recommended

Tension-type headaches

Lifetime prevalence in the general population between 30% and 78%

Begins during the teenage years, a ecting more women than men

Stress-related or associated with MSK problems in the neck

The episodic form is described as typically bilateral, pressing or tightening in quality, of mild to moderate intensity, lasting minutes to days, with no nausea or vomiting

The infrequent subtype occurs <12 days per year, and the frequent subtype occurs 1–14 days per month, on average for 12–180 days per year

The chronic form evolves over time and occurs >15 days per month, on average for >180 days per year

Acute treatment with aspirin, paracetamol, or NSAID is recommended

No pharmacological prophylaxis is indicated, but acupuncture can be considered

Trigeminal autonomic cephalgias

TACs share the clinical feature of lateralizing headaches with prominent ipsilateral cranial parasympathetic features. Di erent subtypes exist with characteristic features

Cluster headache

Age 20–40 years; male:female 3:1

At least ve attacks which are unilateral orbital, supraorbital, or temporal

Severe intensity and variable quality, associated with restlessness or agitation, lasting for 15–180 minutes

Frequency can vary from one every other day to 8/day; episodic: 7 days to 1 year, with remission lasting at least 1 month; chronic: attacks occur for >1 year, without remission or with remission periods <1 month

Other symptoms include ipsilateral conjunctival injection or lacrimation, nasal congestion or rhinorrhoea, forehead and facial sweating or ushing, eyelid oedema, miosis, and/or ptosis

Treatment: acute—oxygen therapy, nasal or SC triptan; prophylactic—verapamil during cluster bout

Paroxysmal hemicrania

Onset in adulthood

At least 20 attacks which can be unilateral orbital, supraorbital, or temporal, lasting for 2–30 minutes

Severe intensity and variable quality

Frequency is about 5/day for more than half of the time; *episodic:* at least two bouts lasting 7 days to 1 year, separated by remission periods of 1 month; *chronic:* attacks without remission or with remission of <1 month for at least 1 year

Other symptoms include ipsilateral conjunctival injection or lacrimation, nasal congestion or rhinorrhoea, forehead and facial sweating or ushing, eyelid oedema, miosis, and/or ptosis

Responds absolutely to indomethacin

Short-acting unilateral neuralgiform headaches

Onset in adulthood

At least 20 attacks which can be unilateral orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1–600 seconds

Moderate to severe in intensity and can be single stab, series of stabs, or saw-tooth pattern

Frequency is 1/day for more than half of the time; *episodic:* 7 days to 1 year, with remission lasting at least 1 month; *chronic:* attacks occur for >1 year, without remission or with remission periods <1 month

Symptoms include ipsilateral conjunctival injection or lacrimation, nasal congestion or rhinorrhoea, forehead and facial sweating or ushing, eyelid oedema, miosis, and/or ptosis

SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing): both conjunctival injection and lacrimation

SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms): only one or neither of conjunctival injection and lacrimation

Treatment is di cult. First line: lamotrigine; second line: topiramate, gabapentin

Hemicrania continua

Onset in adulthood

Attacks should be present for >3 months and are unilateral

Moderate to severe in intensity and of variable quality

Present for >3 months with exacerbations; *remitting subtype:* not continuous pain but has remission of at least 1 day; *unremitting subtype:* daily and continuous for at least 1 year without remission of 1 day

Other symptoms include ipsilateral conjunctival injection or lacrimation, nasal congestion or rhinorrhoea, forehead and facial sweating or ushing, eyelid oedema, miosis, and/or ptosis

Responds absolutely to indomethacin

Medication overuse headache

Headache occurring on 15 or more days per month, developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for >3 months

It usually, but not invariably, resolves after overuse is stopped

A public health problem, with a worldwide prevalence of 1–2%

Aims of treatment are withdrawal of overused drugs, to provide the patient with pharmacological and non-pharmacological support, and to prevent relapse

The Severity of Dependence Scale (SDS) score is a signi cant predictor of medication overuse amongst headache patients

Withdrawal symptoms lasts for 2–10 days after detoxi cation

The most common symptom is initial worsening of the headache, accompanied by various degrees of nausea, vomiting, hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness

The duration of withdrawal headaches has been found to vary with di erent drugs, being shorter in patients overusing triptans (approximately 4 days) than in those overusing ergotamine (approximately 7 days) or analgesics (approximately 10 days)

Improvements are seen in two out of three patients after detoxi cation treatment

Further reading

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2. National Institute for Health and Care Excellence. Headaches in over 12s: diagnosis and management. NICE Clinical Guideline [CG150]. 2021. https://www.nice.org.uk/guidance/cg150
3. Matharu MS, Goadsby PJ. Trigeminal autonomic cephalgias. J Neurol Neurosurg Psychiatry 2002;72(2):19–26

28.5 Orofacial pain

De nition

Pain localized to the region above the neck, in front of the ears, and below the orbitomeatal line, as well as pain within the oral cavity

Comprises a large group of disorders, including temporomandibular disorders (TMDs), headaches, neuralgia, pain arising from dental or mucosal origins, and idiopathic pain

Of speci c note

There is an inherent complexity in shared care, including diagnosis, between dental and medical professionals

An acute dental problem can masquerade as any of the other diagnostic groups, and vice versa, as dental pain can be referred, poorly localized, or misdiagnosed and can become chronic

Common dental conditions may well coexist with other chronic pains

Incidence

12–26% of British adults report >1 day of orofacial pain within the past month

Up to 50% of this is chronic

Classi cation

Dental

Pulpitis

Cracked tooth

Dentine sensitivity

Abscess

Non-dental

(See Table 28.5.1.)

Table 28.5.1 Types of non-dental pain

Oral non-dental pain	Neurovascular and tension	Cranial neuralgia	Persistent idiopathic
1. Oral malignancy 2. Mucosal lesions 3. Salivary gland pathology (lithiasis or tumour) 4. Atypical odontalgia	1. Tension-type headache 2. *Migraine:* i. Neurovascular orofacial pain (NVOP) ii. A subset of migraine usually in the distribution of the trigeminal nerve 3. *Trigeminal autonomic cephalgias:* i. Cluster headache ii. Paroxysmal hemicranias iii. Short-lasting unilateral neuralgiform headaches with conjunctival tearing (SUNCT) iv. Short-lasting unilateral neuralgiform headaches with cranial autonomic features (SUNA) d. Hemicrania continua	*Primary:* 1. Trigeminal neuralgia 2. Glossopharyngeal neuralgia *Secondary:* 1. Post-herpetic neuralgia 2. Diabetes mellitus 3. Multiple sclerosis 4. HIV 5. Post-traumatic neuropathy = anaesthesia dolorosa	1. Temporomandibular joint dysfunction (TMD) = facial arthromyalgia 2. Stomatodynia = burning mouth syndrome 3. Persistent idiopathic facial pain (PIFP) = atypical facial pain (AFP) = atypical odontalgia 4. Giant cell arteritis (GCA)

Diagnosis and triage to appropriate clinician

Based on history, examination, and investigation

Investigation and treatment

Dental

Speci c treatment by a dental surgeon

Non-dental oral

Speci c investigation, including biopsy for histological diagnosis, followed by multidisciplinary discussion to determine the optimum treatment pathway which may include surgery/chemotherapy and/or radiotherapy

Atypical odontalgia

Continuous dull ache or burning pain in teeth (normal or treated teeth), sometimes felt in extracted teeth site, worse on chewing

May spread to neighbouring teeth

Absent radiological ndings

Links with psychological issues, somatization, and other chronic pain conditions

Treatment—reassurance, anti-neuropathics

Neurovascular and tension

(See 28.4 Headaches, p. 561.)

Multidisciplinary pain management input for chronic pain

Tension-type headache

Conservative multidisciplinary treatment

Migraine/neurovascular orofacial pain

Simple analgesics/NSAIDs and antiemetics

Triptans

Prophylactic -blockers, TCAs, topiramate, valproate, gabapentin

Botulinum toxin

Cluster headache

Oxygen

Triptans

Prophylactic prednisolone, verapamil, lithium, methysergide

Paroxysmal hemicrania

Indomethacin

SUNCT/SUNA

Lamotrigine, oxcarbazepine, topiramate, gabapentin

Hemicrania continua

Indomethacin

Cranial neuralgias

Trigeminal neuralgia

(See 24.6 Trigeminal neuralgia, p. 490.)

Multidisciplinary pain management input
Carbamazepine/oxcarbazepine, lamotrigine, pregabalin
Microvascular decompression, RF, or thermal ablative techniques

Glossopharyngeal neuralgia

(See 24.7 Glossopharyngeal neuralgia, p. 494.)

Pain in the soft palate, ear and mastoid, base of tongue, and posterior pharynx, may be triggered by yawning, swallowing, talking, or coughing
Multidisciplinary pain management input
As for trigeminal neuralgia

Post-herpetic neuralgia

(See 24.9 Post-herpetic neuralgia, p. 497.)

One or more dermatomal distributions of the trigeminal nerve can be a ected—second most commonly a ected nerve after thoracic nerves
Ramsay Hunt syndrome—herpes zoster infection of the geniculate ganglion, causing facial palsy with earache
Vaccination against VZV/herpes zoster
Early systemic antiviral medication
Multidisciplinary pain management
TCAs, antiepileptics, opioids, NMDA receptor antagonists, topical lidocaine, capsaicin

Diabetic polyneuropathy

(See 24.13 Diabetic polyneuropathy, p. 509.)

Optimization of underlying diabetes
Multidisciplinary pain management input
Anti-neuropathic medication

Multiple sclerosis-related neuropathy

Optimization of underlying neurological condition
Multidisciplinary pain management

HIV-related neuropathy

Optimization of the underlying condition
Multidisciplinary pain management

Post-traumatic neuropathy = anaesthesia dolorosa

Pathophysiology of anaesthesia dolorosa

Rare dea erentation pain that occurs after traumatic (including radiotherapy) or surgical injury to the trigeminal nerve.
Risk of 1.6% after glycerol rhizotomy, 0.8–2% after RF rhizotomy, and 2% after percutaneous controlled thermocoagulation
Numbness associated with severe disabling pain

Treatment of anaesthesia dolorosa

TCAs

Anticonvulsants

Multidisciplinary pain management

Persistent idiopathic

Temporomandibular disorders

Clinical features

The most common causes of orofacial pain

A ect 10–15% of the population over a lifetime, more in females

Pain localized to pre- and post-auricular areas and the mandible

Unilateral or bilateral, can radiate to the head and neck

Associated clicking or crepitus and locking of temporomandibular joints, with tightness felt around the face

Intermittent or continuous pain, sharp, dull, or shooting in nature

Typically exacerbated by yawning and mastication, can be associated with bruxism

Dysregulation of the adrenergic system with decreased COMT activity may be seen

Risk factors for TMDs

Degenerative TMDs rare but should be excluded, e.g. RA

Higher levels of distress, catastrophizing, and hypervigilance than controls

Linked with anxiety/depression and other chronic painful conditions, including bromyalgia and back pain

Management of TMDs

Rule out red ags (dysfunction of the cranial nerve, sudden onset in >50-year-old patients, extremely limited mouth opening, lymphadenopathy, discharge/bleeding from the nose)

Primarily a self-limiting disorder which should be treated conservatively

Simple analgesics, TCAs, anticonvulsants

Occlusal splints or mouth guards

Multidisciplinary pain management input (education, acupuncture, psychological support, and self-management strategies)

Surgery rarely, e.g. after failure of conservative management, degenerative joint disease, or disc dysfunction

Persistent idiopathic stomatodynia = burning mouth syndrome (BMS)

A benign condition presenting as a burning sensation/pain in the absence of any abnormal clinical ndings in the mouth or abnormal blood tests

Primarily located in the anterior two-thirds of the tongue but can involve the lips, gingivae, and hard palate ± altered sensation of taste

Pathophysiology largely unexplained, but some evidence of small- bre sensory neuropathy ± central changes on fMRI scanning

Commonly presents around/after the menopause and can be associated with anxiety/depression and other benign painful conditions, e.g. bromyalgia, interstitial cystitis, IBS

A ects 2% of the population

Female:male 7:1

Treatment of BMS

Clonazepam (PO or topical)
TCAs
Anticonvulsants
Multidisciplinary pain management

Atypical facial pain (AFP) = persistent idiopathic facial pain (PIFP)

A persistent idiopathic orofacial pain, which does not t the clinical pattern for any other diagnosis, present for 6 months or more
A ects the middle-aged female population, often unilateral
Not restricted by neurological anatomical boundaries
Pain can be deep, vague, wandering, and constant and can extend into the neck
Examination may reveal some areas of decreased sensations in the painful area
Often associated with psychological comorbidity and other chronic benign painful conditions, needing a thorough psychological workup
Treatment outcome is usually unsatisfactory; along similar lines to trigeminal neuralgia, but evidence base weak as heterogeneity of patients and rarity of the condition limit research opportunities. TCAs and anticonvulsants may help and invasive interventional procedures should be avoided

Giant cell arteritis

Important di erential diagnosis in patients over 50 years
Daily headaches, sensitivity in the scalp, generalized fatigue ± pain in the tongue
Throbbing, continuous temporal, or pre-auricular pain
Usually unilateral
Reduced pulse in a dilate, tortuous temporal artery on examination suspicious
Blood ESR can be markedly elevated, and CRP and temporal artery biopsy diagnostic
Potentially vision-threatening, so requires urgent diagnosis and treatment with high-dose steroids (if necessary before test results back)
Biopsy can be positive within 7–10 days of starting steroids
Urgent referral to ophthalmology
May be associated with jaw claudication, systemic illness, and polymyalgia rheumatica
Giant cell arteritis can be active for up to 2 years; hence, steroids should be continued to prevent vision complications

Further reading

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28.6 Paediatric chronic pain

Introduction

Paediatric chronic pain is increasingly recognized

However, chronic pain in children has been less extensively studied and the evidence base is smaller than in adults

Pain in neonates was only recently recognized and many procedures were done without any analgesia or anaesthesia in the past

Pain pathways and mechanisms in children

Pain pathways in children di er functionally from those in adults due to a maturing nervous system:

- Little descending inhibition from higher CNS centres in the rst week
- Dendritic spine density 2–3 times of that of adults
- Highest dendritic spine density in the prefrontal cortex at 2.5–7 years
- The RVM switches from a facilitator of nociception to an inhibitor with age
- Animal studies show that the PAG area does not produce analgesia at early ages

Prolonged neonatal intensive care is associated with increased nociceptive sensitivity, and fMRI studies show increased central sensitivity of brain pain pathways

Epidemiology of paediatric pain

(See Table 28.6.1.)

A cross-sectional Dutch study of 5425 children showed that 54% experienced pain within the last 3 months and 25% su ered from chronic pain of >3 months' duration (8% of this pain was described as severe). Girls were more likely to su er from chronic pain than boys

Pain assessment

(See Table 28.6.2.)

Assessment of pain is age-dependent, and both self-reporting and physiological measures are commonly used

Assessment must be age-appropriate and younger children may not easily verbalize or self-report their pain

Table 28.6.1 Epidemiology of paediatric pain

Pain type	Prevalence (%)	Age
Headache	8–82	Older
Abdominal	3.8–53.4	Younger
Back	13.5–24	Older
Musculoskeletal	3.9–40	Older
Multiple	3.5–48.8	Unknown
Other	5–88	Unknown

Table 28.6.2 Pain assessment in children

Pain	Pain intensity Pain description Temporal aspects
Associated symptoms	Fatigue Sleep
Emotional	Anxiety Depression
Cognitive	Coping Catastrophizing Avoidance
Social	School attendance Family function Parental anxiety and depression

Therapeutic basis of management

Paediatric chronic pain requires a multidisciplinary approach and a biopsychosocial model is the current model of care

Evidence for the use of adult management strategies is limited in the paediatric population

Strategies must be age-appropriate and the impact of pain on the family is a signi cant consideration in long-term management

Speci c pain presentations

Although many chronic pain syndromes are present in both the paediatric and adult populations, there are important differences in their presentation, aetiology, and prognosis

Complex regional pain syndrome

Peak incidence is in early adolescence, with a female predominance

Compared with adults, there is a greater incidence in the lower limb, but prognosis is better

Fewer physical signs are present

Diagnostic criteria are similar to those for adult CRPS using the Budapest criteria (see 24.11 Complex regional pain syndrome, p. 501)

Initial management is with physiotherapy, and this is associated with a good outcome in 90% of patients

Refractory cases bene t from an interdisciplinary approach

The role of interventions (nerve blocks, neuromodulation) is unknown and its use must be combined with a multidisciplinary pain management strategy

Neuropathic pain

Due to the immaturity and capacity for plasticity of the nervous system, neuropathic pain has a number of signi cant di erences in childhood

Many medical conditions seen in adults are uncommon in children such as diabetic neuropathy and PHN

Obstetric brachial plexus palsy is rarely associated with neuropathic pain

The incidence of neuropathic pain after never injury is lower in children and approaches adult levels after adolescence

Post-surgical neuropathic pain is increasingly recognized in children (after inguinal hernia repair, 13.5% of children reported chronic pain and 2% described it as severe in intensity)

The proportion of SCI patients who are paediatric is 3–5%

Neuropathic pain is less common in children, compared with adults

Injury in under 20-year olds have a 26% risk of developing persistent pain, whereas the risk is 45% in those above 20 years of age

Anti-neuropathic analgesia (e.g. TCAs and gabapentinoids) are useful adjuncts in children and doses must be age-appropriate

- Gabapentin (5–10 mg/kg three times daily)
- Amitriptyline (0.5 mg/kg at night)

S/Es must be balanced with analgesic bene t, as CNS S/Es can have signi cant e ects on school and exam performance

Topical therapies such as lidocaine plasters or 8% capsiacin are especially useful due to their lack of systemic e ects

Abdominal pain

A high proportion of abdominal pain in children is associated with a functional cause

The diagnosis is made on the basis of:

- Episodic or continuous pain
- Insu cient criteria for other functional GI disorders
- No evidence of in ammatory, anatomic, metabolic, or neoplastic processes that can explain the symptoms

Functional abdominal pain includes IBS, functional dyspepsia, and abdominal migraine

Apart from abdominal migraine, symptoms must be present for at least 8 weeks

Despite a lack of organic pathology, a ected children have frequent school absences, functional impairment, and psychological distress with depression and anxiety

Although pharmacological approaches are common, there is a lack of evidence of their long-term e cacy

CBT has been associated with bene cial outcomes

Headache

Headache in children is among the most common causes for medical consultations in children

The diagnostic criteria for migraine are modi ed

Ages a ected

All ages are a ected by headache:

- 3–8% by 3 years of age
- 20% by 5 years
- 37–51% by 7 years
- 57–82% by 15 years

Important causes

Although there are a large number of diagnoses, the important causes are:

- Migraine (most common cause of chronic daily headache)
- Medication overuse headache (second most common cause)

Tension-type headache and new daily persistent headache
TAC

Features that indicate imaging

Recent onset of severe headache
Change in severity or frequency
Fixed or unusual location
Early morning or waking from sleep
Postural headache
Abnormal neurological examination
Abnormal growth or puberty
Deterioration in school function

Management principles

Although medication is the most common approach, it is important to balance the risk and bene ts
Excessive use of analgesia can result in analgesic overuse headache, and opioids must be avoided
Lifestyle management, education, and behavioural therapies are important in long-term management
The use of occipital nerve blocks can be a useful and low-risk adjunct

Musculoskeletal pain

Most MSK pains in children are benign, but a full assessment is crucial to rule out in ammatory arthritis, infection, and malignancy
About 7–15% of all schoolchildren su er from MSK pain
Back pain is an increasingly recognized problem in children
By the age of 18 years, at least half will have reported episodes of back pain, but few of these will present themselves to health professionals
It is important to rule out serious pathology, and a careful clinical assessment is required to make a diagnosis and to identify red ags that may constitute serious underlying pathology
Radiological imaging often starts with plain radiographs to look for infections, structural abnormalities, and tumours
Further imaging (CT or MRI) can then be used if appropriate
Most mechanical low back pain responds to physiotherapy, but refractory cases will bene t from a multidisciplinary approach
The role of interventions is limited and their use is less than that seen in adults

Important causes of back pain in children

Intervertebral disc pathology

Disc degeneration is seen in 6–19% between 10 and 18 years of age
It is possible that many cases of adult back pain start in childhood

Scheuermann's disease

Presents with thoracic and thoracolumbar kyphosis
Symptoms improve with skeletal maturity
Refractory cases may bene t from spinal bracing

Juvenile idiopathic arthritis

Commonly a ects the cervical spine

In older children, SIJ pain may be present

Osteomyelitis and discitis

Infants and children di er from adults in that the disc has widespread anastomotic channels

This allows for pyogenic osteomyelitis and TB to occur in the spine, but also decreases the risk of infarction and increases the chance of bacterial clearance

Unlike in adults, discitis in children is often self-limiting and an infectious cause is uncommon

Neoplasia

Nocturnal pain and progressive increase in symptoms should alert the clinician

Conclusions

Chronic non-cancer pain is increasingly recognized as a signi cant cause of functional impairment and disability in children

It has an impact on the child's QoL, school performance, and peer networks

Therapy must be aimed at recognizing the di erences in the aetiology and natural history of pain in children, with an understanding of the complex relationships involving their family, school, and social networks

A multidisciplinary biopsychosocial approach should be applied, as single interventions are often insu cient

Further reading

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28.7 Pain in the elderly

Introduction

Chronic pain prevalence increases with age—chronic pain a ects 63% of patients over 75 years of age

There is an increased prevalence of chronic pain in care home residents (>80% compared with >50% in the community)

Chronic pain in older adults tends to be constant, of moderate to severe intensity, and lasting for several years (multifocal and multifactorial)

Persistent pain or its inadequate treatment is associated with a number of adverse outcomes in older people, including functional impairment, falls, slow rehabilitation, mood changes

(depression and anxiety), decreased socialization, sleep and appetite disturbance, and greater health care use and costs

Aetiology

The most common sites of chronic pain in the elderly are the hips, knees, and back

Pain conditions which are more common in older adults include:

- MSK—myofascial pain syndrome, OA
- Cancer-related—due to cancer itself and/or cancer treatments
- Neuropathic—peripheral neuropathies, PHN, post-stroke pain
- Other— bromyalgia

Physiology/psychology

A meta-analysis showed that while pain threshold increases with age, pain tolerance thresholds do not show age-related changes. Therefore, ageing reduces pain sensitivity for lower pain intensities

Some studies suggest an increased vulnerability amongst older adults to severe and persistent pain

Psychological factors may a ect pain reporting in older adults, including altered pain beliefs and attitudes, fear of addiction, misattribution of symptoms, and stoicism

Risk factors

Loneliness and social isolation

There is a strong link between pain in the elderly and low mood—each being a risk factor for the other

Increased risk of mood disorder, cognitive decline, and falls in elderly patients with chronic pain

History

Assessment of pain in older adults may be more di cult due to communication issues (visual/hearing loss), concurrent illness, cognitive ability, and socio-cultural factors

Patient self-reporting of pain is the most valid and reliable indicator of pain, even in the presence of mild to moderate dementia—the NRS or verbal descriptors should be used to establish pain intensity

A self-report measure of function should also be used such as the Pain Disability Index

For patients with severe cognitive impairment (e.g., scoring <18 on Mini-Mental Status Examination), the PAINAD, Abbey or Doloplus-2 scales are recommended. Also gain a history from carers/family members to determine the patient's function, rest, leisure, and productivity

The PAINAD scale involves observation of the patient for 3–5 minutes during an activity to note breathing, negative vocalizations, facial expressions, body language, and consolability. Each domain is scored 0–2, with a total possible score of 10

Comorbidities may contribute to pain or in uence the treatment of pain

Drug history essential to anticipate potential drug–drug interactions

Examination

In addition to a general examination, including cardiorespiratory, consider the following speci c examinations:

- Neurological—central, peripheral, and autonomic nervous systems
- MSK and rheumatological—look, feel, move joints and muscles

Assessment of mobility/balance—impacts on falls risk

Assessment of mental state especially the cognitive function

Investigations

Imaging only indicated for patients in whom there is suspicion of a disease which requires specialist intervention, e.g. hip OA, neurogenic claudication, etc.

Consider imaging in the presence of 'red flags', e.g. worsening pain with a history of cancer, risk factors for infection (e.g. immunosuppressive therapy), constitutional signs/symptoms, recent trauma or risk of fractures

Treatment

General principles

Stepped approach—the least potentially toxic interventions should be used initially, followed by therapies with greater risks

Systemic medications are used as a later step due to the risk of S/Es, toxicity, and interactions with other medications used for chronic illness

Local treatments/topical treatments may be preferable due to lack of systemic S/Es

High risk of drug–drug and drug–disease interactions in patients on multiple medications for other comorbidities

Altered pharmacokinetics with ageing include:

- Absorption: altered from the gut due to slowing of GI transit time (may increase absorption of continuous-release enteral drugs)
- Distribution: altered due to increased fat:lean body weight ratios
- Metabolism: altered due to altered function of the hepatic system and CYP450 enzymes
- Excretion: due to reduced glomerular filtration and renal clearance

Pharmacological treatments

Paracetamol

Well tolerated

Caution in dosing for low-weight elderly adults

NSAIDs

Should be used with great caution in elderly adults—risk of adverse effects significantly higher in older adults, especially those with chronic kidney disease, gastropathy, and cardiovascular disease, or those who may be intravascularly deplete, e.g. heart failure.

If used, use at the lowest dose for the shortest period of time, co-prescribed with a proton pump inhibitor

Naproxen and celecoxib have been shown to be the most appropriate of NSAIDs for patients with cardiovascular risk factors

COX-2 selective inhibitors have a lower risk of GI S/Es, but cardiovascular risk factors are higher

Opioids

Effective in the short term (<12 weeks), but long-term data are lacking

May be appropriate in moderate to severe pain in highly selected patients with functional impairment or impaired QoL

Modi ed-release or transdermal preparations aim to provide relatively constant plasma concentrations for continuous pain, although short-acting opioids are preferred to reduce opioid induced ventilatory impairment and other opiod related adverse e ects

Risk of S/Es will necessitate antiemetic and laxative co-prescription. May also a ect level of consciousness/thinking processes and increase the risk of falls

Caution in renal failure with renally cleared drugs, e.g. hydromorphone/morphine/oxycodone

Adjuvant medications

Primarily used for neuropathic pain

Use at the lowest dose and titrate upwards slowly to the lowest e ective dose

Caution with tramadol and TCAs which have anticholinergic S/Es (sedation, cognitive dysfunction, orthostatic hypotension)

Caution with pregabalin and gabapentin especially in renal impairment—risk of S/Es: dizziness, somnolence, fatigue, cognitive impairment, falls, peripheral oedema, depression

Carbamazepine/oxcarbazepine may be used for trigeminal neuralgia—risk of hyponatraemia/SIADH

Duloxetine—evidence e ective for treatment of neuropathic pain and some studies suggest use for non-neuropathic pain, e.g. OA/lower back pain

Topical treatments

Lidocaine/capsaicin/menthol—limited e cacy for management of localized neuropathic pain but have a good safety pro le with minimal adverse e ects

Topical NSAIDs for localized MSK pain

Pain interventions

Use in older population—evidence is weak/mixed/lacking

Procedures most commonly performed:

- Intra-articular injections of corticosteroids/hyaluronic acid, e.g. knee OA
- Spinal nerve blocks for degenerative lumbar disease/spinal stenosis

Other procedures:

- Condition-speci c neural blocks
- Percutaneous procedures for trigeminal neuralgia in elderly patients with comorbidities
- Epidural corticosteroid injections, e.g. spinal stenosis—limited evidence (less evidence in radicular pain/sciatica)
- Facet joint injections/RF denervation of medial branch nerves
- Sympathectomy—weak evidence in older population for neuropathic pain

Physical treatments

Must be tailored and individual-speci c to optimize function and independence

Aim to strengthen the core, improve exibility and endurance for physical activity, improve function, and reduce falls risk

Use of assist devices to enable engagement in ADLs may enable the patient to remain more independent and reduce functional decline

Psychological treatments

Aim to in uence how people respond and cope with pain

CBT improves chronic pain, disability, and mood

Limited evidence for biofeedback training, relaxation, mindfulness, meditation, and enhancing emotion regulation in elderly patients with chronic pain

Complementary therapies

Limited research for e ectiveness of TENS/massage/re exology/acupuncture in elderly with chronic pain

However, anecdotal evidence suggests some bene t

Interventional/surgical treatments

Vertebroplasty/kyphoplasty for the treatment of acute painful vertebral fractures

Joint replacement for OA

Further reading

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28.8 Human immunode ciency virus

Introduction

The HIV targets the immune system and weakens people's defence systems against infections and some types of cancer

Undertreatment of pain in HIV patients is common, particularly in patients with less education and a history of IV drug use, and in females

Incidence

Globally, 36.7 million people were living with HIV at the end of 2016, with 1.8 million people becoming newly infected. An estimated 0.8% of adults aged 15–49 years are living with HIV worldwide; 54% of adults and 43% of children living with HIV worldwide are currently receiving lifelong antiretroviral therapy

Approximately 30–60% of patients have severe pain associated with a profound negative impact on psychological and physical functioning, as well as on overall QoL. Prevalence of poorly controlled pain has been reported in up to 97% of terminally ill HIV patients

Patients are more likely to be unemployed and disabled and to have less social support

Patients with HIV who experience pain are more likely to be distressed, depressed, and hopeless and to have suicidal thoughts (40%), compared to those without pain (20%)

Aetiology of pain

Direct damage caused by HIV

Immunosuppression

Therapies for HIV/acquired immunode ciency syndrome (AIDS)

Associated disorders with HIV/AIDS

Causes unrelated to HIV/AIDS

A review found the mechanisms of HIV-related pain were 45% somatic, 15% visceral, 19% neuropathic, and 4% unknown

Pain syndromes in HIV patients

Nervous system

Neuropathies

Distal symmetrical polyneuropathy and antiretroviral toxic neuropathy are the most common

Acute herpes zoster, acute varicella zoster, and post-herpetic neuropathy are also common

Others: autonomic neuropathy, acute zoster pain, post-herpetic neuropathy, mononeuritis multiplex, mononeuropathies, di use in ammatory lymphocytosis syndrome, lumbo-sacral polyradiculopathy, demyelinating polyradiculoneuropathy, HIV-associated neuromuscular weakness syndrome

Brain disorders

HIV encephalopathy: aseptic/bacterial/viral (cytomegalovirus (CMV) or HIV)/fungal (*Cryptococcus*)

Toxoplasmosis

Malignancies: lymphoma, sarcomas such as Kaposi's or others

Other conditions such as migraines, tension headaches, and sinusitis

Gastrointestinal system

Oral cavity: oral lesions, infections (*Candida*), mouth ulcers

Oesophagitis related to infections or HIV therapies

Infections: gastroenteritis, hepatobiliary, etc.

S/Es of medications

Peptic ulcer disease

Pancreatitis

Neoplasms: Kaposi's sarcoma, non-Hodgkin's lymphoma, and others

Anorectal pain

Cardiothoracic system

Pneumonia (commonly *Pneumocystis carinii*), lung malignancy

Endocarditis, pericarditis, myocarditis, especially in patients who use IV drugs

Rheumatic system

Reiter's syndrome, septic arthritis, psoriatic arthritis

Polymyositis from HIV itself or from medications (e.g. azathioprine)

HIV-associated sensory neuropathy

Most common cause of peripheral nerve dysfunction in HIV (between 30% and 60% of individuals a ected)

Two clinically almost indistinguishable entities, with di erent causes, often coexisting:

- Distal sensory polyneuropathy (HIV-related)
- Antiretroviral toxic neuropathy (antiretroviral treatment-related)

Clinical presentation

Distal symmetrical small- bre neuropathy in a 'stocking and glove' distribution, with the feet being a ected rst. Progressive onset of symmetrical paraesthesiae, numbness, and painful dysaesthesia of the lower extremities. Hyperalgesia and allodynia are common

Descriptors used by patients are commonly 'burning', 'numb', and 'tingling'

Wearing shoes can become problematic, although some patients report the most pain when they are barefoot in bed (allodynia provoked by contact with linen)

As the course of the disease progresses, the symptoms can ascend to the legs

When the pain reaches the knees, the upper limbs may become involved (ngertips)

Hypore exia of the lower extremities is common (reduced/absent Achilles re ex)

Weakness is rare (if it occurs, explore alternative diagnoses)

Insidious onset for distal sensory polyneuropathy; sudden and rapidly progressive onset for antiretroviral toxic neuropathy, temporally associated with exposure to antiretroviral therapy (as early as 1 week from the start, and usually within the rst year of use). These are the only true di erentiating elements

Pathophysiology

Distal sensory polyneuropathy: neuronal apoptosis induced directly by the Gp120 HIV protein, and exposure of Schwann cells and macrophages to Gp120 results in the release of neurotoxins

Antiretroviral toxic neuropathy: exposure to nucleoside reverse transcriptase inhibitors (NRTIs), in particular stavudine, didanosine, and zalcitabine, can lead to mitochondrial toxicity and resulting nerve damage

In both of these neuropathies, there is distal axonal degeneration and dying-back axonopathy of long axons a ecting both myelinated and unmyelinated bres

Risk factors

Advanced HIV disease: low CD4 T cell count, high viral load

Exposure to NRTIs and neurotoxic medications (antibiotics, chemotherapy)

Diabetes, hypothyroidism, hypovitaminosis (especially B12)

Increasing age and height (longer nerve bres)

Alcohol and recreational drug use

Concurrent infections (hepatitis C, syphilis)

Diagnosis

Mainly based on history, clinical picture, and physical examination

Investigations:

- To screen for other causes
- Electrodiagnostic studies warranted in cases of weakness or asymmetry (may point to other types of neuropathy)
- Biopsy (tissue, sural nerve)—not routine clinical practice and commonly in research

Management

Prompt initiation of HIV treatment in antiretroviral-naïve patients

Change to non-neurotoxic agents in patients on treatment

Mitigation of other sources of nerve insult (see Risk factors, p. 580)

Physical, pharmacological, and psychosocial interventions as per general pain management principles

Pharmacotherapy that can be used:

Anticonvulsants: gabapentin, pregabalin, lamotrigine

Antidepressants: amitriptyline, nortriptyline, duloxetine, venlafaxine

Topical: lidocaine 5% patch, capsaicin 8% patch or topical 0.0075% or 0.0125%

Cannabis (evidence is controversial and is unlicensed in many countries for chronic non-cancer pain management)

Opiates to be used with great caution as:

There is little evidence for e cacy of opioids in HIV neuropathic pain

There is a high risk of opioid misuse or abuse in HIV patients

Opioids may have pro-nociceptive e ects (activation of glia, secretion of pro-nociceptive mediators such as cytokines, ILs, TNF) and may promote HIV infectivity from opioid-related immunosuppressive e ects

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28.9 Sickle cell disease

De nition of sickle cell disease

Inherited autosomal recessive disorder of the Hb molecule

The normal glutamic acid is replaced by valine on the -globin gene, producing a variant Hb called HbS

Homozygotes have sickle cell disease, and heterozygotes have sickle cell trait

HbS in combination with other variants produces Hb-thalassaemia

The major sequelae are haemolysis, anaemia, and pain

Incidence

Incidence 1/5000—the most common severe genetic disease in the UK

More common in African, Afro-Caribbean, Asian, Mediterranean, and Middle Eastern people

Carriers exhibit partial resistance to all forms of *Plasmodium falciparum* malaria

Physiology

HbS causes the red cell to become sickle-shaped and in exible under certain physiological conditions

'Sickle cells' cause microvascular occlusion and increased haemolysis

Pain in sickle cell disease

Acute painful crises:

Vaso-occlusion leads to a combination of hypoxia–reperfusion injury, ischaemic tissue damage, and chronic vascular in ammation

In ammatory mediators, especially ATP, H^+, and glutamate, activate receptors on A-delta and C- bres within the nociceptive system

Chronic pain:

In ammatory response secondary to repeated episodes of microvascular occlusion and resultant tissue damage

Central sensitization and 'wind-up' of the nervous system in response to recurrent acute painful crises, causing long-term amplification and maintenance of the pain signal

Neuropathic pain:

Putative mechanism is via microvascular occlusion of the vasa vasorum

Common presentations include mental neuralgia, trigeminal neuralgia, and more rarely orbital or spinal cord infarction

Risk factors for acute painful crises

Acidosis, hypoxia, exposure to cold, exercise, stress

Frequent, severe acute painful crises with inadequate analgesia increase the risk of chronic pain

Diagnosis

Hb electrophoresis

Screening of at-risk pregnant women and their partners in early pregnancy to detect carriers

Heel-prick blood spot test in newborns in the UK

Perioperative screening of high-risk patients for sickle cell trait

Treatment

Supportive treatment:

Balanced diet, sleep, hydration, folic acid, regular surveillance. Multidisciplinary input to address the sequelae of chronic pain and illness

Symptomatic management:

Blood transfusion for anaemia, analgesic plan for acute painful crises, as well as for chronic pain, antibiotics for infection

Preventative management:

Prophylactic daily penicillin V until age of 5, pneumococcal vaccination, stress management, HbF induction with hydroxyurea, avoidance of precipitating conditions

Abortive management:

Prompt, aggressive treatment of acute painful crises

Blood parameters can support the diagnosis of acute painful crises (decreased red blood cell (RBC) deformability, increased number of dense cells, reticulocytes, leucocytes, and relative thrombocytopenia) in complex cases, e.g. to exclude opioid-seeking behaviours

Provide a pain management plan for patients to institute at home (commonly short-acting opioids and paracetamol)

Treat preferably in a rapid access medical day case admission unit rather than via the emergency department

Future avenues include anti-adhesion molecules and inhaled NO

Curative therapy:

Stem cell transplantation, future gene therapy

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2. Brousse V, Makani J, Rees DC. Management of sickle cell disease in the community. BMJ 2014;348:g1765

28.10 Vascular insu ciency pain

Introduction

A number of terms describe a spectrum of peripheral vascular disorders:

- Peripheral arterial disease—a disease of the peripheral arterial system characterized by insu cient blood ow to the limbs to support normal function
- Intermittent claudication—a clinical syndrome that consists of leg pain induced by walking; the pain improves with rest
- Critical limb ischaemia—persistent pain at rest due to insu cient blood supply to a limb, leading to poor tissue perfusion, tissue loss, skin ulceration, and loss of limb function
- Acute limb ischaemia—an acute emergency caused by sudden loss of blood supply to a limb, leading to rapid tissue loss and limb function

Incidence

Age-related increase in prevalence of up to 15% of the population aged above 50 years

Important modi able risk factors include poor nutrition, smoking, diabetes, hypertension, obesity, high alcohol use, and hyperlipidaemia

Pathophysiology

Reduction of blood ow causing a mismatch between the supply of nutrients and the removal of toxic metabolites from tissues by:

- Atherosclerotic plaque causing arterial stenosis or occlusion (most common mechanism)
- Embolization of an artery from a thrombus or arterial dissection perioperatively

Nociceptive and/or neuropathic pain plus autonomic dysfunction

History

Assess the psychological, physical, and social impact of the pain on the person and the functional limitations as a result of the pain. Characteristics of vascular insu ciency pain:

- Nature of the pain:
  - Ischaemic pain is normally worse on elevation and relieved by dependency. In critical limb ischaemia, there is rest pain and/or claudication pain (exacerbated by exercise and immediately relieved by rest)
  - Neuropathic pain can present as burning, altered sensation, shooting, or allodynia, and may be worse at rest and relieved by exercise
  - Nociplastic pain: mixed presentation of nociceptive and neuropathic pain
- Time frame can be acute, subacute, or chronic
- Can a ect sensory (small or large bres), motor, autonomic, or multiple nerve bres
- Distribution most commonly:
  - Aorto-iliac disease manifesting with pain in the thigh and buttock
  - Femoral–popliteal disease presenting as pain in the calf

Examination

Cardiorespiratory examination focusing on the peripheral vascular system

Relevant examination for other causes as infections, ulcers, haematomas, compartment syndrome, deep vein thrombosis, etc.

Assess for signs of:

- Ischaemic limb—hair loss, shiny skin, skin ulcer, pale skin colour, brittle nails, weakness, weak/absent peripheral pulses, sensory loss, and muscle wasting
- Neuropathy—large, small, motor, autonomic fibre involvement with sensory gain or loss and pattern (polyneuropathy, mononeuropathy, symmetrical)

Investigations

Psychometric questionnaires—e.g. BPI, Depression Anxiety Stress Scales (DAAS), the Leeds Assessment of Neuropathic Symptoms and Signs (LANNS) Pain Detect, Neuropathic Pain Questionnaire (NPQ), Identification Pain Questionnaire (ID Pain)

Blood tests—FBC, lipid profile, metabolic and diabetic screen

Ankle–brachial pressure index <0.8 indicates significant peripheral artery disease

US Doppler study

CT angiogram or MRI

Angiogram and interventional radiology

Differential diagnosis

Lumbar spinal canal stenosis—this produces neurogenic claudication

CRPS

Phantom limb pain

Spinal cord, lumbar plexus, and peripheral nerve palsy

Idiopathic

Other causes of peripheral neuropathies such as metabolic (e.g. diabetes), toxic (e.g. alcohol, antineoplastic agents, antiretrovirals), autoimmune (e.g. lupus, vasculitic neuropathy), infective (e.g. HIV), and inherited (e.g. hereditary sensory neuropathy, Fabry's disease)

Treatment

Disease-specific treatments

Healthy diet, smoking cessation, BP, exercise, and weight optimization

Statins and antiplatelet agents

If conservative treatments fail to improve QoL and function, consider:

- Minimally invasive endovascular revascularization—angioplasty, stenting
- Open bypass operations
- Amputation

Multidisciplinary treatments

Address physical, psychological (psychiatric or psychological), and social (work, litigation, social support network) contributors to pain, disability, and distress:

- Patient education is one of the primary goals to empower patients to adapt and achieve QoL that is as optimal as possible
- Development of pain management strategies (e.g. activity pacing, exercises, desensitizing, goal setting, thought challenging, and others)

CBT, ACT, cognitive restructuring, distraction, relaxation, mindfulness, and other psychological strategies individually or in a pain programme according to the patient's needs

Pharmacological treatment

Several agents can be considered, including:

- Anticonvulsants (e.g. gabapentin, pregabalin)
- Antidepressants (e.g. TCAs, SNRIs, SSRIs)
- Opioids (e.g. tramadol, tapentadol, morphine)—no long-term studies showing e cacy
- Other medications with lower evidence include ketamine, lidocaine, topical capsaicin, and IV PG

Pain intervention

Subarachnoid, epidural, or peripheral nerve blocks—e ective in acute limb ischaemia

Sympathetic block for critical limb ischaemia:

- Lumbar sympathetic block has inconsistent results for lower limb pain
- Stellate ganglion block for upper limb ischaemic pain has variable success

SCS—RCT has shown bene t for peripheral vascular disease and refractory angina. The British Pain Society guidelines recommend these as good clinical indications for SCS. SCS could not be recommended by NICE due to inadequate RCT data and insu cient economic evaluation

Further reading

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SECTION 6

CANCER AND PAIN

CHAPTER 29

Cancer and Pain

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29.1 Cancer pain mechanisms

Introduction

Cancer pain is a complex syndrome involving in ammatory, neuropathic, and ischaemic mechanisms, and most patients experience mixed pain (80%)

30% of patients at an early stage of cancer su er from pain, increasing to 75–90% in advanced stages

Types of pain

Neuropathic pain

Due to damage to neurons, either peripheral or central, via mechanical compression, ischaemia, haemorrhage, chemical changes, and oedema, further impeding oxygen supply, and transection

There is peripheral and central sensitization, leading to spontaneous and ectopic discharges and activation of NMDA receptors

In ammatory pain

Peripheral and central mediators of in ammation, such as bradykinins and cytokines, establish a feed-forward loop that results in sensitization of primary a erents, recruitment of silent nociceptors, and peripheral hyperalgesia

Nociceptive/visceral pain

Di use, poorly localized pain with symptoms of spasm and heavy feeling. It can be secondary to bowel obstruction or ischaemic bowel

Pain due to direct e ect of malignant tumours (70%)

Deposits of abnormal cancer cells are very active metabolically and divide rapidly, which causes an imbalance between oxygen supply and demand, causing necrosis. These cells secrete a large amount of pain chemical mediators such as TNF alpha, NGF, and ILs, leading to an in ammatory response attracting lymphocytes and macrophages

Tumour expansion and fascia and capsular stretching, causing mechanical pressure locally

Direct mechanical compression, in ltration, or entrapment of nerves and plexuses, causing neuropathic pain and direct in ltration of tissues, bone, and viscera

Obstruction of hollow viscus and blood vessels results in in ammation and ischaemia. This causes di use pain due to peritoneal stretching

Bone metastasis

Metastatic disease of bone is a very common cause of severe pain and occurs in nearly 90% of patients, mainly arising from cancers a ecting the prostate, breast, lung, kidney, and thyroid gland, and spreads to the axial skeleton, ribs, arms, and long bones of the leg

Increased osteoblastic activity in the bone leads to enhanced structure of the bony matrix, causing periosteal stretch pain. Increased osteolytic or bone destruction activity of the bone marrow a ects and destroys the sensory nerve endings and causes neurochemical reorganization of the spinal cord

Increased bone loss due to resorption of bone by osteoclasts causes painful pathological fractures in patients with advanced disease:

- Paraneoplastic phenomenon causing the production of antibodies against neurons, leading to peripheral neuropathy or neuritis
- Secondary infection and open ulcer formation

Pain related to cancer therapy (20%)

Chemotherapy

Chemotherapeutic drugs can be neurotoxic, especially vinca alkaloids (vincristine, vinblastine); alkylating agents containing platinum (cisplatin, carboplatin, oxaliplatin); and paclitaxel, docetaxel, and bortezomib causing peripheral neuropathy and mucositis

Steroids can cause osteonecrosis; immunocompromised individuals can have infections (herpes zoster)

Neurotoxicity is dose-dependent and worse when used in combination

Radiotherapy

Radiation causes in ammation, brosis, and necrosis, as well as injury to the peripheral and central nervous systems, causing severe neuropathic pain, plexopathies, myelopathy, osteonecrosis, mucositis, and cystitis

Surgical

Pain due to neuroma formation, post-thoracotomy pain syndrome, post-mastectomy pain syndrome, phantom pain

Pain due to other factors (10%)

Impaired mobility resulting in decubitus ulcer and bedsores

Constipation, dehydration, and OIH

Psychological stress

Cancer-associated symptoms, such as malaise, cachexia, anxiety, and myofascial dystrophy, aggravate pain symptoms

Pre-existing medical conditions such as arthritis, low back pain, migraine, and bromyalgia

Characteristics of cancer pain

Cancer and its metastatic disease are progressive and dynamic, in comparison to CNCP which is static. This may lead to requirement of escalated and higher doses of potent opioids

Cancer pain can occur from diagnosis till the end and can range from procedural/surgical pain initially to treatment-related pains, pain due to metastasis, and nally pain at the end of life. Another entity seen is pain in long-term survivors a ecting their QoL

People with cancer pain su er from depression and psychological stress, in addition to physical discomfort—hence, psychological elements, such as depression, anxiety, and stress, pose more challenges in pain management

Cancer patients su er from other disabilities such as insomnia, cachexia, nausea and vomiting, dysphagia, constipation, anorexia, skin conditions, and complications of treatment

Identifying speci c pain associated with speci c neoplasm helps in o ering e ective therapy at an early stage and preventing pain and su ering later, e.g. brachial plexopathy secondary to Pancoast tumour extension, lumbo-sacral plexopathy secondary to colorectal or prostate tumour extension or metastases from the breast

Breakthrough pain is any transient and clinically signi cant pain that rises over adequately controlled baseline pain. It a ects roughly about two-thirds of patients with cancer pain and is associated with more severe pain, reduced response to opioid medications, increased psychological distress, and worsening functional impairment

Incidental pain which occurs due to movement, e.g. unstable pathological fractures

Further reading

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29.2 Overview of cancer pain management

Assessment of cancer pain

Adequate and regular reassessment of cancer pain, with accurate documentation, should be carried out in order to provide optimal treatment

Comprehensive assessment of this pain using a multi-dimensional model, with assessment of the underlying disease

History and examination to con rm the presence of background, incident, or breakthrough pain should be obtained

Include the type of pain and its intensity and localization, along with aggravating and relieving factors, the presence of neuropathic pain, and current management of pain relief

A thorough psychological, social, and spiritual assessment using assessment tools prior to initiating a management plan. Assessment of other cancer-related symptoms, especially anxiety, depression, and sleep disturbances, which can a ect the patient's family relationships and QoL

Knowledge about the patient's coping strategies, economic impact, and spiritual beliefs can in uence the treatment plan

Newer-onset pain or change in pain should be addressed immediately and investigated, as it may highlight worsening in the patient's condition or worsening of existing pain needing analgesic modi cation

Management of cancer pain

A biopsychosocial approach, rather than simply following the WHO ladder, should be used. Care of a patient su ering from cancer pain requires a holistic approach, combining psychological support, social support, rehabilitation, and pain management, in order to provide the best possible QoL or quality of death.

Principles of cancer pain management

Education

Explaining to patients the cause of pain and the treatment options available, as well as their adverse e ects, to help the patient manage their condition in a better and more satisfactory way

Modi cation of pain threshold

Improving activity, mood, sleep, and social support can work positively towards raising the pain threshold in these patients

Situations which increase pain may need to be avoided

Patients need to plan ahead and may need aids to change their lifestyle to reduce pain

Physiotherapy and OT play a very important role in recognizing and minimizing the impact of the disease on the day-to-day functioning of the patient

Lifestyle modi cation

Situations which increase pain may need to be avoided

Patients need to plan ahead and may need aids to change their lifestyle to reduce pain

Physiotherapy and occupational therapy play a very important role in recognising and minimising the impact of the disease on the day to day functioning of the patient

Oncological management

Anti-cancer treatment signi cantly helps in relieving pain either by treating the cancer or by palliation

Themainapproachestoshrinkthesizeof thetumourandmetastasisare:

Surgery may be indicated for various procedures, e.g. stabilization of pathological fractures, resection of necrotic tumours, drains and shunt surgery for ascites and obstructive hydrocephalus

Hormone therapy has been shown to have good results in patients who have hormone-sensitive tumours such as prostate and breast cancers

Chemotherapy—patients with widespread metastases respond well to chemotherapy if the tumours are chemosensitive. Multiple myeloma and bronchus and breast cancers respond well to this modality of treatment

Radiotherapy—radiation produces free electrons and free radicals which destroy tumour cells and decrease pain; it can be delivered either systemically with radionuclides or as external local- eld or wide- eld radiotherapy. Osteoblastic lesions respond very well to radiotherapy

Modi cation of pain perception

Perception of pain can be modi ed through pharmacological, as well as non-pharmacological, methods

Non-pharmacological methods—heat and cold therapy, acupuncture, TENS

Complementary therapies—improve well-being: aromatherapy, homeopathy, herbal medicines, hypnotherapy, massages, re exology relaxation, and music therapy

Pharmacological management

Systemic analgesics are considered the first-line treatment modality for cancer pain, with opioids being the ideal systemic medication

It should be via an oral route, unless not tolerated or inadequate, and customized to the patient's requirement, ranging from simple non-opioid analgesics for mild pain to weak opioids, such as codeine, for moderate pain and strong opioids, such as morphine, for moderate to severe pain, and should provide background analgesia, as well as rescue analgesia

It is important to monitor both short- and long-term S/Es of the drugs and treat aggressively

Interruption of pain pathways by interventional therapies

Neuroablation can be carried out by longer-lasting nerve-blocking procedures—either physical (heat, cold, mechanical pressure, surgery) or chemical (alcohol, phenol, glycerol)

This works well for localized pain along the distribution of a nerve or nerve plexus

Psychological interventions

Some patients benefit from psychological interventions such as coping skills training, attention diversion strategies, and cognitive coping strategies

The WHO ladder has significantly helped in cancer pain management but is not without limitations. We need to embrace a new model of management, which uses multimodal combination therapies, is mechanism-based, and includes interventions to optimize pain relief and limit adverse effects

The Sheffield model of care encompasses the above and recommends pain therapies throughout the illness by using: (1) disease-directed therapy; (2) patient-directed therapy; and (3) family-directed therapy (see Figs. 29.2.1 and 29.2.2)

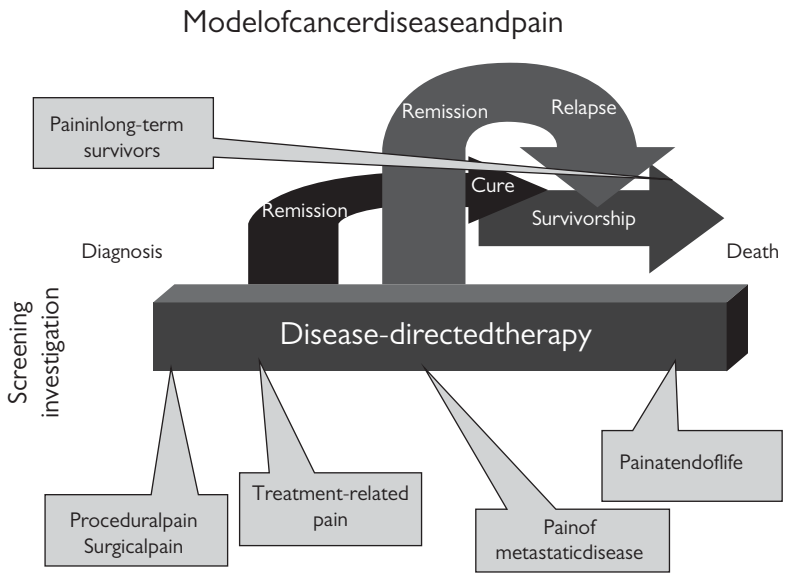


Figure 29.2.1 Cancer disease and pain

Adapted with permission from Ahmedzai, S., H. and Walsh, D. (2000). Palliative medicine and modern cancer care. *Seminars in Oncology*, 27(1): 1–6

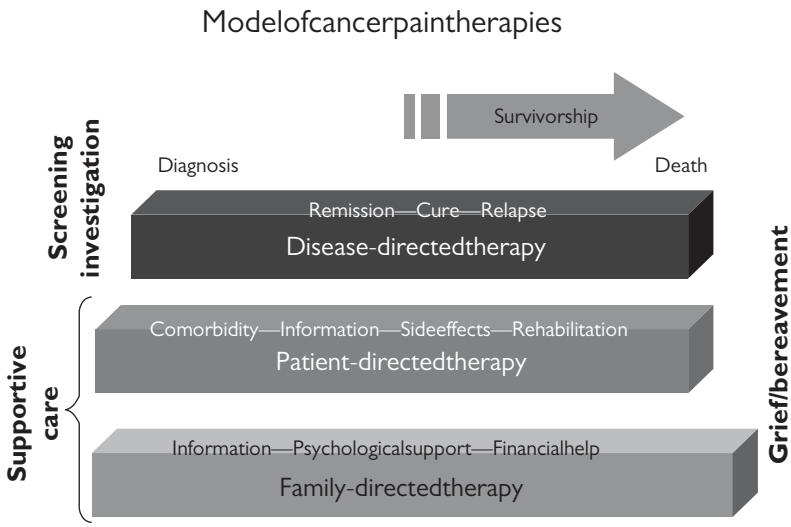


Figure 29.2.2 Pain therapies for cancer

AdaptedwithpermissionfromAhmedazai,S.,H.andWalsh,D.(2000).Palliativemedicineandmoderncancercare. *SeminarsinOncology* ,27(1):1– 6

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29.3 Cancer pain and psychology

The diagnosis of cancer can have a massive psychological impact on both the patient and the family

They su er from grief, anxiety, depression, and psychological stress, in addition to physical discomfort, which can cause signi cant challenges in management, especially at certain points such as at diagnosis, start of treatment, relapse or recurrence, and treatment failure, and at the thought of dying

Psychological distress, such as worries about death, pain, family issues, and nancial strain, exacerbates the pain and, in turn, further worsens the psychological disturbances

Fear can generate high anxiety, resulting in poor coping strategy, and reduces the threshold for pain

25% of cancer patients su er from **depression**, which results in feeling of worthlessness, impaired concentration, and disinterest in daily activities. Depressed patients may develop hopelessness and helplessness

Management

Assessment of psychosocial factors in uencing the experience of pain will include the patient's understanding of their condition, what the pain means to the individual and their family, how

the pain may impact upon relationships within the patient's family, whether the pain in uences the patient's mood, coping strategies adopted by the patient, and the patient's sleep pattern

Proper assessment of emotional and psychological status of cancer pain patients is an essential step in management

The HADS is very helpful in quantifying the impact. Counselling, relaxation, and education reduce anxiety in cancer patients

Psychological approaches in pain management include coping skills training, attention diversion strategies, and cognitive coping strategies. They teach the patients various behavioural and cognitive skills to cope with their pain and reduce their physical and psychological distress

Pain management programmes aim to help the patient improve their QoL and achieve optimal functioning despite their medical conditions. CBT has been shown to produce promising results for cancer pain management in the acute period

Palliative care in managing other symptoms associated with cancer

Palliative care is de ned as active total care of patients whose disease is not responsive to curative treatment. The goal is to achieve the best QoL for patients and their families

Management of other symptoms causing distress in cancer patients, which include constipation, general weakness, cachexia, dry mouth, oral ulceration, disabilities related to malignant in ltration such as paraplegia and bowel obstruction, anorexia, and dyspnoea, as well as familial and social distress

A multidisciplinary team with di erent specialists and allied health professionals is essential to palliative care

The She eld model of supportive care is a good multimodal, comprehensive model of cancer pain management

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29.4 Opioids and adjuvants in cancer pain management

Since 1986, the WHO's 3-step analgesic ladder has been widely adopted as a simple guideline for cancer pain management, based on the recommendations of an international group of experts. It relied on a simple, stepwise escalation of treatment, resulting in adequate pain relief in 70–80% of patients

Opioids

Opioids are the most important option in cancer pain management and all patients with pain should be o ered a trial

Highly e ective in somatic and visceral pain in the short and medium term

Helps with neuropathic pain relief at su ciently high doses, although not recommended

Regulatory barriers still prevent access to opioids due to potential misuse and addiction in many countries

Principles of opioid administration

The goal—a balance between clinically signi cant, sustained pain relief and S/Es with improved QoL

Traditionally, pure mu agonist opioids were used in cancer pain management, whether weak (codeine) or strong (morphine)

Partial mu agonist drugs, such as buprenorphine, have a limited role due to their analgesic ceiling e ect and potential precipitation of withdrawal e ects in patients already on strong opioids

Drugs with a mixed action acting centrally through the noradrenergic pathway, such as tramadol and tapentadol, may play a role

Drug selection

Opioids are selected according to intensity of pain—codeine or low-dose morphine for moderate pain, and morphine, oxycodone, fentanyl, oxymorphone, and hydromorphone for severe pain

Opioids with short t1/2 are used rst due to ease of titration

Increasingly, methadone is being used for cancer pain management due to high oral bioavailability, longer dosing intervals, absence of active metabolites, long t1/2, cheap costs, and dual mechanism of action as a mu receptor agonist and NMDA antagonist

The equianalgesic dose conversion relationship between morphine and methadone is curvilinear (methadone: morphine)

Low-dose oral morphine (30–300 mg) 1:4–1:6

High-dose oral morphine(>300 mg) 1:10–1:12

Opioid rotation

Some patients may not respond to a particular type(s) of opioids, su er from adverse e ects, or become opioid-tolerant successive trials of di erent types until one with a favourable response is identi ed is known as *opioidrotation*

Due to incomplete cross-tolerance between different opioids and receptor polymorphism

Automatically cause a 25–50% reduction in the equianalgesic dose of the chosen opioid

Increase or decrease by 15–30% and prescribe 5–15% of the total daily dose for breakthrough pain

Routes of administration

Ideally the least invasive and painful, most reliable, and safest route. Oral route whenever possible

If vomiting or pathology involving the bowel, other routes could be chosen

Transdermal route: fentanyl patches are an important advancement in cancer pain management and cause less constipation

Rectal route: almost equianalgesic to the oral route. Oxycodone, oxymorphone, hydromorphone, and morphine suppository formulations exist

Invasive routes: if need for rapid control of pain, more suitable regimen, and very high opioid requirements oral route not practical

Intermittent or continuous infusions via IV or SC routes are most commonly used. The IM route is painful with no pharmacological advantage

SC infusion ± *PCA*: through a 25–27G device such as a 'butter y'. Could infuse opioids + other drugs such as ketamine and antiemetics. Oxymorphone, hydromorphone, morphine, diamorphine, and fentanyl are suitable as they are absorbable, and soluble methadone is not recommended due to its irritating e ect

Neuraxial infusion

Scheduled administration

'Around the clock': regular, preferably with controlled-release preparations continuous sustained pain relief with provision of as needed (PRN) or 'rescue doses' 50–100% of 4-hourly dose or 5–15% of total dose/24 hours

PRN dosing: as sole regimen, useful during initiation of opioid therapy until stabilized on opioid therapy

Dose titration

Doses increased by 30–100% of xed dose or by an increment equal to the total consumed as 'rescue doses' in the previous 24 hours divided over the xed dose

Assess e ect of each increment: 2–3 days for modi ed-release preparations, 3–6 for patches, and 5–6 for methadone

Breakthrough pain

Short-acting drug on a PRN basis, opioid, or opioid–non-opioid drug combination

Transmucosalfentanyl —speci cally indicated due to rapid absorption faster pain relief

Opioid side e ects

Nausea, vomiting, and constipation: worse in this cohort due to immobility, poor diet, abdominal pathology, polypharmacy

Respiratory depression: tolerance develops over time

Somnolence and mental clouding, due to high doses used, could be compounded by other factors related to disease, e.g. metabolic derangement or cerebral tumour. Patients may bene t from a psychostimulant such as dexamfetamine or methylphenidate 2.5–10 mg once or twice daily

Delirium and confusion: compounded by other factors, such as somnolence, and can be managed by a small dose of a neuroleptic drug, e.g. haloperidol

Multifocal myoclonus: can cause breakthrough pain; could bene t from opioid rotation, BZD, or an anticonvulsant

Other S/Es include urinary retention, hypogonadism, dry mouth, pruritus, disorientated sleep, tolerance, and OIH. OIH is treated with gradual dose reduction, opioid rotation, or an alternative strategy other than opioids

Adjuvant analgesics

Adjuvants for neuropathic pain

Antidepressants: such as TCAs, e.g. amitriptyline and imipramine. Secondary amine TCAs, such as nortriptyline and desipramine, have fewer S/Es. Starting dose 10–25 mg; aim for 75–125 mg/day. Also used are selective serotonin–noradrenaline reuptake inhibitors (SSNRIs), e.g. duloxetine

Anticonvulsants: gabapentinoids especially useful. Some clinicians use carbamazepine, based on favourable experience with trigeminal neuralgia

LAs: topical lidocaine such as 5% patches, oral mexiletine

Adjuvants for bone pain

Usually treated by a combination of GCs and bisphosphonates. Bisphosphonates: inorganic analogues of pyrophosphate inhibition of osteoclast activity. Pamidronate at a dose of 15–30 mg/2 weeks or 60 mg/4 weeks (more e ective)

Adjuvants for visceral pain

Oxybutynin: useful in bladder spasm pain due to anticholinergic and papaverine-like antispasmodic e ect

Octreotide: a somatostatin analogue useful in inoperable bowel obstruction

Anticholinergics (hyoscine): useful for inoperable bowel obstruction

Multipurpose adjuvants: breakthrough pain

GCs, such as dexamethasone and prednisolone, have been shown to result in analgesic bene t and improved QoL. Their e ects include reduction of oedema, in ammation, and stabilizing electrical activity in a ected nerves

Useful in conditions such as headache caused by raised ICP, acute spinal cord compression, and hepatic capsular distension

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29.5 Neurolytic procedures for cancer pain management

Introduction

The WHO analgesic ladder forms a useful framework for initial cancer pain management

10–15% of patients with pain that is poorly responsive to opioids, or where S/Es are particularly problematic, may greatly bene t from invasive procedures designed to interrupt pain signals along neural pathways

Such procedures should not be seen as the 'fourth step' on the WHO analgesic ladder but can, and should, be considered at each step, depending on patient preference and need

Various methods are used for neurolysis (see Table 29.5.1)

Table 29.5.1 Methods used for neurolysis

Pharmacological	Physical	Surgery
Alcohol (50–100%) Phenol (3–12%) Glycerol Ammonium sulfate	Heat—alternating current of 50–100 kHz, producing lesions causing neuroablation; thermocoagulation Cold—cold saline, cryoprobe Mechanical—balloon compression for Trigeminal nerualgia	Rare, e.g. midline myelotomy, presacral neurotomy

Intrathecal neurolytic or neuro- destructive lesions

Corning in 1884 reported the use of IT cocaine; however, it was Dogliotti who first described the use of IT alcohol for chronic pain management in 1931

Since then, many authors have described IT injection of various neurolytic substances for treatment of oncologic pain

Maher in 1955 suggested the use of phenol in glycerine

Other chemical agents, such as chlorocresol, ethyl ether, ammonium salts, silver nitrates, and hypertonic saline, have been used

By the mid- twentieth century, central neuraxial techniques were associated with significant incidences of infection due to poor aseptic practices, which led to poor acceptance of central neuraxial procedures for pain relief

In recent years, alcohol and phenol have been the substances most commonly used for this purpose

There are no controlled studies, so the literature consists of observations, reports, and book chapters reflecting the opinions of experienced clinicians

Use of neurolytic blocks is particularly relevant if pain does not respond to analgesics, S/Es of analgesics are intolerable, or the IT catheter technique for cancer pain relief is not an option

Intrathecal thoracic/cervical neurolytic block

IT thoracic/cervical neurolysis can be used to relieve unilateral intractable malignant pain in upper thoracic and/or lower cervical dermatome

At lower thoracic dermatomal levels, the spinal cord level does not correspond quite well to the vertebral level, and therefore, deciding about the level at which injection is required to be performed, to address pain, is quite challenging

The presence of the denticulate ligament, a fibrous structure separating the sensory (dorsal) and motor (ventral) fibres of the spinal nerves as they emerge from the spinal cord, and the baricity of the injected neurolytic solution allow to target selective sensory nerve fibres by positioning the patient appropriately

The patient is placed in a lateral position at a 45° semi-prone angle if a hypobaric drug is used or in a lateral position at a 45° semi-supine angle if a hyperbaric neurolytic solution is injected intrathecally

The procedure is performed with aseptic precautions and under fluoroscopy guidance

A 22G, or narrower-gauge, spinal needle is used

Usually 0.2 mL of neurolytic solution for each dermatome is used and no more than 0.8–1 mL should be injected at a single level, to minimize the risk of inadvertent spread to motor nerve roots

Dehydrated alcohol (50–100%) is generally used for IT thoracic/cervical neurolysis as it is hypobaric and oats in the CSF, blocking only sensory bres in the painful (upper) side

It is also less uncomfortable for the patient to lie on the non-painful side while in a lateral position at a semi-prone angle

The patient should be warned about a burning sensation in the painful area which occurs immediately on injection of alcohol intrathecally, which settles down gradually over a few minutes

After injecting alcohol and prior to withdrawal, the spinal needle should be ushed with about 0.3 mL of plain bupivacaine to avoid alcohol tracking back in its path

The patient is then kept in same position for at least 30 minutes, so that alcohol xes to sensory bres only

Intrathecal saddle block

IT saddle neurolytic block is e ective in managing pain in the perineum related to pelvic organ malignancy

Phenol with glycerol is hyperbaric, as compared to the CSF, and available in various concentrations ranging from 5% to 10%

Being a saddle block, it a ects both sensory and motor components of the sacral nerves and therefore can a ect bowel and bladder sphincters, causing incontinence

However, often due to the nature of malignancy, patients usually have either a stoma and/or a urinary catheter *insitu*, and incontinence as a complication of the procedure is not always a signi cant issue in most patients

Phenol with glycerol is a highly viscous solution, hence the need of a wider-gauge spinal needle (22G or 20G)

Injection is performed at the lowest possible (L5/S1 or L4/L5) vertebral level in the sitting position, tilted at 45° backwards, which is maintained for at least 30 minutes after injection of phenol, so that only the lower sacral nerves are blocked

Dose 0.1–0.3 mL aliquots up to a volume of 1 mL to be injected. If patient has urinary and faecal incontinence, then a higher dose could be used. Motor function should be monitored at all times when injecting the drug

Mechanism of action of intrathecal neurolytic block

Experimental animal post-mortem studies suggest that neurolytic solutions cause demyelination and degeneration of nerve bres

Although they a ect all types of nerve bres indiscriminately, the degree of destruction depends on the concentration of the agent used

A ected nerve bres do eventually regenerate, and therefore, the e ect of the neurolytic agent usually lasts for 10–12 weeks only

Informed consent

For any neurolytic procedure, it is mandatory that realistic success rates, common S/Es, and complications are discussed with the patient/family members

The patient also should be provided with written information lea ets, as most patients requiring these blocks are often on high doses of opiates and neuropathic agents and therefore may not completely understand only verbal explanation of the procedure/its complications

The patient should be made aware of failure of the procedure, loss of touch/temperature sensation in the blocked area, undesirable adjacent/motor nerve blockade, dea erentation pain, and infection

It is also important to inform the patient that these blocks may not relieve all the pain and may not be e ective beyond a few months, requiring a repeat of the procedure, if appropriate

Post-procedure

Haemodynamic changes are minimal following the above-mentioned IT neurolytic blocks

Transient weakness may occur which usually improves in a few days

Once pain reduction is achieved, patients on high-dose strong opiates and neuropathic agents may become stuporous with respiratory depression

Careful close observations for the rst 24 hours at least (hospice/hospital) and changes to the usual doses of strong opiates may be warranted

Epidural or intrathecal drug delivery systems

(See 20.5 Epidural injections, p. 377; 29.6 Intrathecal drug delivery treatment for cancer pain, p. 602.)

Used when patients are opioid-responsive but struggle with S/Es at higher opioid doses

Can be externalized systems or implanted systems which deliver pharmacological agents such as background infusions ± intermittent boluses

Cordotomy

(see 20.7 Percutaneous cordotomy, p. 382.)

Creation of RF lesion in the lateral spinothalamic tract at the C1/2 level on the opposite side of pain, eliminating pain and temperature sensations from half of the body

Midline myelotomy

A surgical technique, which involves sagittal division of the spinal cord in the lumbar region for severe pelvic pain as it disrupts the spinothalamic tracts

Rarely done as causes paralysis and incontinence

Vertebroplasty and kyphoplasty

(See 22.9 Vertebroplasty, p. 438.)

Performed for vertebral body disease where cement is injected into the vertebral body under uoroscopy

Neurolytic/neuroablative procedures of peripheral nerves/plexus and visceral blocks

Can be performed with pharmacological and RF lesioning

Nerve root blocks, brachial/lumbar plexopathy, e.g. tumour in ltration

Intercostal nerve block, e.g. phenol for rib metastasis

Paravertebral blocks

Coeliac and splanchnic plexus blocks, e.g. chemical neuroablation for pancreatic cancer

Hypogastric blocks, e.g. abdominopelvic malignancies

Ganglion impar blocks, e.g. perineal pain

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29.6 Intrathecal drug delivery treatment for cancer pain

Analgesia is achieved by direct deposition of the drug into the CSF through continuous infusion

It avoids the BBB, hence allowing the use of small doses

This a ords a reduction in S/Es and possibly a quicker and more e cacious response

ITTD allows the use of LA infusions in the management of cancer pain

Various receptors, such as opioid receptors (MOP, KOP, and DOP), NMDA, GABA, Na+, Ca^{2+}, dopaminergic, and -2, can be targeted within the DH of the spinal cord

It could be achieved through either an external device or a fully implantable pump

Although a subject of debate, the common practice is to perform a trial infusion before proceeding to full implantation

(See also 20.8 Intrathecal drug delivery systems, p. 384)

External ITDD

There are two external methods of delivery:

- One connected to a percutaneous catheter that may or may not be tunnelled. This is more suitable in patients with limited life expectancy
- The other is a completely implanted catheter that has an SC port connected to an external pump. This is more suitable in patients with a short life expectancy

Usually performed percutaneously under uoroscopy guidance

The medication could be either infused continuously or administered intermittently

Drugs commonly used

Morphine, ziconotide, LAs, and others such as ketamine, adenosine, octreotide, neostigmine, midazolam, baclofen, and clonidine, have been tried

Various combinations have been used

NICE and National Health Service England (NHSE) guidance on ITDD

NHSE will routinely commission this service for patients with severe cancer pain that is refractory to conventional pain management techniques, after an appropriate selection process

Evidence suggests that ITDD is a cost-e ective analgesic management strategy, compared to standard opioid treatment, in these patients after 6 months of therapy

Patients will need a comprehensive multidisciplinary team assessment with pain management, oncology, and palliative care

It is an option for patients who have exhausted other options and/or are intolerant of the systemic S/Es of systemic analgesics and after a successful IT opioid trial, if appropriate

Class 1 evidence for clinical e cacy in cancer pain

Management of a patient with an ITDD system

Based upon the dosing regimen, a plan should be made about the re ll intervals, documented, and handed over to the team looking after the patient

A plan should be in place to manage common S/Es of the drugs used in the pump, with adequate provision of drugs that might be needed

It is highly recommended that all clinicians inserting the ITDD system and involved in managing the patient should familiarize themselves with the particular pump being used, its make and model, and its manual

Pump-related failures

Pump: a well-known, preventable cause of pump failure is corrosion, most likely resulting from infusing o -label drug preparations that could result in stalling. This has led Medtronics to issue a notice against the use of unapproved drug combinations. This could result in either withdrawal symptoms or uncontrolled pain, or overdosing

- Pump–catheter misconnection: more common soon after implantations, yet could manifest late
- Loss of pump propellant: resulting in either reduced delivery, manifesting as withdrawal and aggravated pain, or overdosing
- Motor stalling due to gear shaft wear: resulting in slowing of infusion

Catheter: by far more common as they are more vulnerable:

- Migration: resulting in CSF leakage which could result in a hygroma
- Kinking: which could take place anywhere between the pump and the catheter-receiving device. It is evidenced by inability to aspirate or inject
- Drug leakage: which may occur at the pump–catheter connection. It could be immediately post-insertion or delayed
- Microfractures, breakages, occlusion, and in ammatory mass

Symptoms of ITDD failure due to the catheter are usually subtle and primarily noticed and reported by the patient in the form of inadequate analgesia or possibly withdrawal

Workup to identify the cause should start with the history and complaint and then work its way logically

First start by identifying the position of the catheter spread and the ow rates

To explore possible catheter dislodgement or migration, proceed with AP and lateral X-rays

If the catheter is accessible (such as through a port or in the case of external devices), then an attempt should be made at aspirating and injecting under strict aseptic precautions to prevent introducing infection

A minimum of 1.5 mL should be aspirated to remove any drug

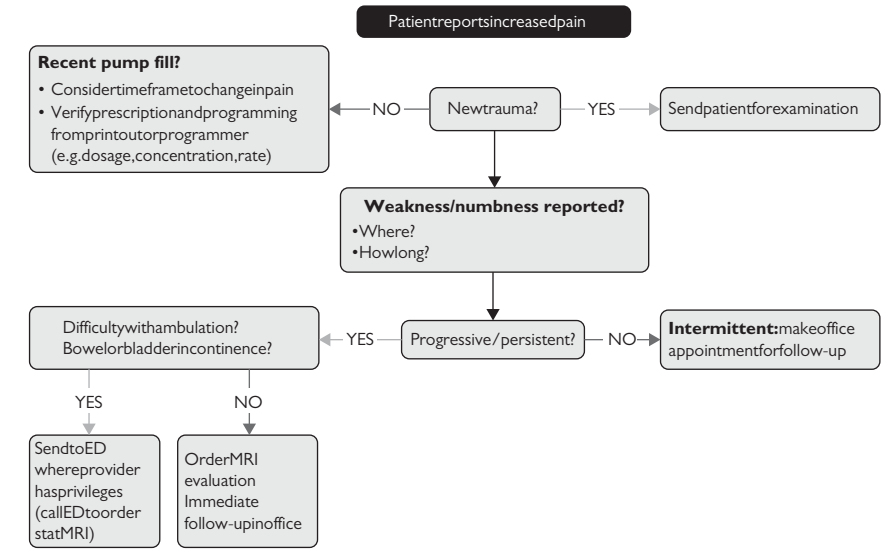
Ease of aspiration: 2–3 mL of CSF is easily aspirated, such that it is unlikely that the tip is obstructed

Holes in the catheter: interrupted ow on CSF aspiration

A total of 2–4 mL of contrast is used to identify the catheter tip location after aspirating the active drug

Radioactive indium: this is the most informative test of catheter integrity. This is reserved for stable patients where catheter withdrawal is not planned in the next 24–48 hours

(See Figs. 29.6.1 and 29.6.2 for management of patients who report increased pain)



B.Officevisit

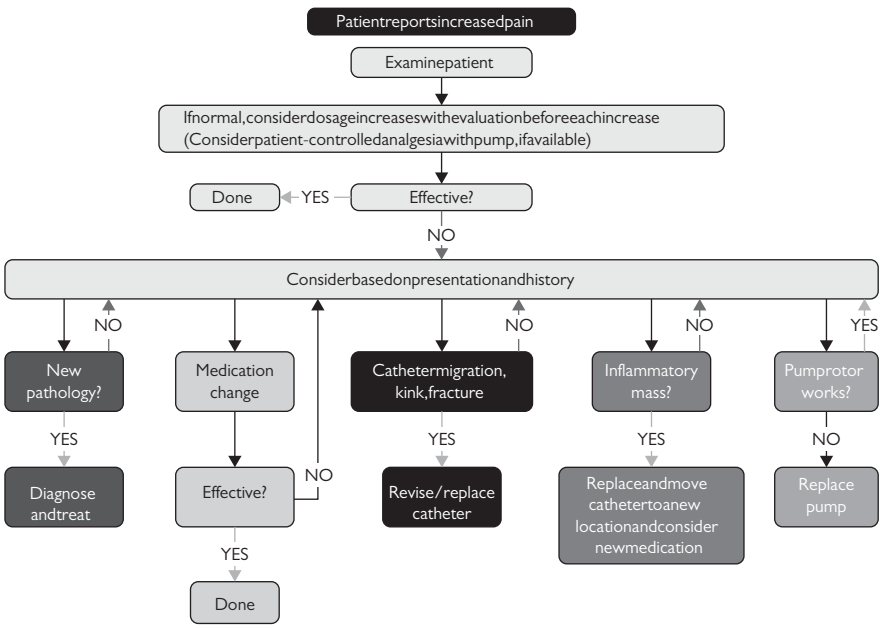


Figure 29.6.1 Flow chart for the management of patients who report increased pain

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Conceptual framework for diagnosing and managing inadequate analgesia
office visit considerations

C. Office visit

History:
- If original presenting pain condition has worsened: neurological changes?
- If new pain: what is quality, intensity, location?
- Do medication adjustments improve or not improve pain?
- In what dermatome is catheter tip located?
- History of pump regarding accuracy of medication remaining?

Physical:
- Neurological exam at presumed catheter tip location and at pain location: evaluate gait, balance, and sensory changes
- Mental status - is patient sedated? Cognitively intact? Agitated? Having hallucinations?

Pump:
- Can CSF be withdrawn through the catheter access port?
- Is a bolus dose effective?
- Is bolus painful?
- Are there any volume discrepancies?

Drug:
- Is the medication in the pump?
- Is refill medication as ordered?
- Have medications been administered within the stability specifications?
- Consider possibility of diversion of pump medication?

Radiologic workup:
- Catheter tip location: has location shifted? Catheter location to be used to determine location for thin slice study; see below
- Catheter access port contrast study: can CSF be easily aspirated? Can contrast be injected and visualized? Is there pain with the contrast injection?
- Imaging study in reservoir versus catheter?
- T1 MRI with gadolinium (thin slice) or CT myelogram to rule out inflammatory mass
- Consider MRI/CT to evaluate new pain location and dermatome level if granuloma workup is negative
- Does pump rotor work (movement can be visualized with CT)?

Figure 29.6.2 Flow chart for the management of patients who report increased pain
Reproduced courtesy of Medtronic. https://www.medtronic.com/uk-en/index.html

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29.7 Chemotherapy for cancer pain

Introduction

Chemotherapy is treatment of disease by use of chemical substances, especially treatment of cancer with cytotoxic and other drugs. The aim of chemotherapy is based on one of the following three therapeutical e ects:

1. Cure: to destroy cancer to the point of being undetectable, with the hope of no recurrence in the future
2. Control: to keep cancer from spreading to other parts of the body or to slow progression
3. Palliate: to ease symptoms related to malignancy, shrink/downsize tumours that cause pain or pressure on critical structures, or improve QoL

Chemotherapy can have one of the following three intents:

1. Neoadjuvant: to reduce the size before de nitive surgery or radiotherapy
2. Adjuvant: to destroy any residual microscopic cells following surgery or radiotherapy, increasing the chance of cure
3. Palliative: to relieve symptoms of cancer or potentially extend life without the intention to cure the disease

There are many agents used for a variety of cancers, which may include chemotherapy, hormonal therapy, tyrosine kinase inhibitors, immunological/biological agents, and bone-modifying drugs. Some of these agents result in predictable S/Es that can cause pain, especially painful neuropathies

The role of chemotherapy for pain management

Malignancy does not always cause pain, but it can be painful, especially if critical structures are involved, or in ltrated or compressed by a lesion, or there is metastatic deposit. Chemotherapy itself rarely causes pain and treatment can often be the best option for pain related to progressive cancer. Chemotherapy can provide e ective analgesia when the cancer burden/volume is high and the tumour is chemo-, immune-, or hormone-sensitive, e.g. extensive small cell lung cancer, neuroendocrine tumours, multiple myeloma, metastatic melanoma, hormone-sensitive breast cancer, or bony lesions from prostate cancer

If cancer responds to chemotherapy, it is important to sequentially reduce analgesia as the cause of pain is removed. Risk of addiction in cancer pain is low, but opioid safety and a weaning plan should be part of regular management, especially in patients with the potential for cure or long-term survival, e.g. localized sarcoma. Opioid minimization strategies are associated with fewer S/Es and there are increasing concerns about opioids stimulating cancer growth (in animal studies)

Pain is not always a sign of cancer being poorly controlled—it should be addressed as an issue of its own, separate from cancer progression (this must be excluded) or treatment. Widespread pain may be a manifestation of existential distress, for example.

Patients who receive support from well-resourced and multidisciplinary palliative care teams experience less pain at their end of life, so advocating for early referrals to the palliative care team is an important strategy in pain management in advanced disease. This allows for not only good symptom management, but also management of psychological, social, carer, and spiritual needs, as well as advance care planning and planning for bereavement support

Chemotherapy causing pain

Chemotherapy infusions are usually painless. Some chemotherapy agents can cause a stinging/burning sensation in the arm during infusion, but this should be mild and subside with infusion. If any pain, check for extravasation, which can be a severely painful event. Acute chemotherapy S/Es can include nausea and vomiting, diarrhoea, mucositis, and very rarely enteritis and typhlitis (if severe toxicity, often accompanied by severe neutropenia). These can lead to issues with absorption of regular analgesics and medications, requiring conversion to SC or IV administration

Myalgias, arthralgias, and headaches can also occur, e.g. with taxol and many hormone-blocking agents. In the medium term, especially if the tumour is particularly responsive to treatment, pain crisis or pain are-up post-treatment can occur (acute swelling with tumour death). Tumour lysis syndrome (renal failure post-extensive tumour lysis) is of particular concern, especially in haematological malignancies. Immune therapies can cause a cytokine storm, requiring signi cant support in the intensive care unit (ICU) setting

Cancers can cause bone complications, causing signi cant disability and movement-related pain. Cancers causing lytic lesions can cause pathological fractures and crush fractures of vertebral bodies. Long-term use of aromatase inhibitors for hormone-sensitive breast cancer can lead to osteopenia and later to osteoporotic (non-malignant) fractures, arthralgia, and myalgia. Management of cancer bone pain includes paracetamol, NSAIDs, opioids, and adjuvants. Current medical management also includes bisphosphonates (pamidronate, zoledronic acid), denosumab, and rarely calcitonin (usually for resistant malignant hypercalcaemia). Vertebral deposits can lead to malignant spinal cord compression (not always painful). It is essential to order full-spine MRI, rather than single-level MRI (i.e. lumbo-sacral MRI) if malignant spinal cord compression is a clinical concern as it can often be multi-level. A review of patients with malignant spinal cord compression identi ed cancer at thoracic (77%), lumbar (29%), cervical (12%), and sacral (7%) levels, as well as at multilevel (25%). Some patients need surgery which can have a curative or symptom control intent (see 24.5 Cauda equina syndrome, p. 489)

In the long term, some chemotherapies can lead to painful peripheral neuropathy and paraesthesiae (numbness), and altered taste, smell, and hearing. Platinum drugs (cisplatin > carboplatin), taxanes (paclitaxel > docetaxel), and vincristine are commonly prescribed chemotherapies that can cause neuropathy. Treatment options include pregabalin, gabapentin, duloxetine, amitriptyline, opioids such as tapentadol, and methadone. Most patients get better with time, over many months in most cases (requiring weaning of medications as symptoms settle)

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29.8 Radiotherapy for cancer pain

Introduction

Ever since its discovery in around 1895, the analgesic e ect of ionizing radiation has been well documented

Hence, radiotherapy is used for the dual purpose of oncological treatment, whether to achieve cure or palliation, and subsequently for its analgesic e ect

It o ers a quick, e ective, and relatively cheap method of managing the *focal* symptoms of advanced malignancy whether due to primary disease or metastases

In advanced malignancy, up to 70% of cases have shown bone metastases on post-mortem studies

The analgesic e ect is achieved through a reduction in tumour mass size, hence decreasing its in ltration and pressure

This may be due to decompression of nerves and nerve plexuses, such as the brachial plexus in Pancoast tumour, or decreased irritation and stretching of periosteal nociceptors in osseous tumours

Mechanism of action and delivery methods

Methods of delivery include percutaneous radiotherapy, radionuclide therapy, stereotactical thalamotomy, and radiodissection of the pituitary gland

Percutaneous radiotherapy—the most common method

High-energy X-rays targeted at the tumour result in cellular DNA damage and eventually death

Linear accelerators are used for its delivery in specialized centres

It could be either:

- Curative: delivered daily in multiple small doses called 'fractions', with the aim of avoiding as much as possible damage to adjacent normal tissues
- Palliative: using lower doses with the primary aim of symptom control

60% of patients treated with palliative radiotherapy gain an element of pain reduction within 2–3 weeks on average

Common indications

Bone metastases

Locally advanced thoracic cancer

Malignant spinal cord compression resulting in pain and neurological symptoms

Brain metastases

Head and neck cancers

Advanced pelvic cancers

Side e ects and complications

Dependent on tissues receiving the treatment and on adjacent normal tissues

Common examples:

- Bone: up to 35% may experience a are-up in the rst week
- Oral cavity and oropharynx: mucositis and pharyngitis (63%), with dysphagia and risk of aspiration pneumonia
- Brain: fatigue and headache (32%) are the most common. The patient may also su er from nausea, vomiting, and otitis externa in a minority of cases
- Lung: coughing

Mediastinum: oesophagitis with resulting dysphagia in up to 22% of lung cancer patients and 28% of oesophageal cancer patients

Stomach and bowel: nausea, diarrhoea, and discomfort

Bladder: frequency, nocturia, and dysuria

Skin: erythema and hair loss

Fatigue: common—up to two-thirds of patients may complain of it

Long-term S/Es are rare, with acute ones resolving within 4–6 weeks of treatment

They are managed by supportive measures to treat symptomatically, with opioids and antiemetics forming the mainstay of treatment

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29.9 Palliative Surgical Procedures

Introduction

Palliative care is de ned by the WHO as an approach that improves the QoL of patients and their families facing problems associated with a life-threatening illness, through the prevention and relief of su ering by means of early identi cation and appropriate assessment and treatment of pain and other physical, psychosocial, and spiritual problems

There are several surgical procedures that may be helpful in improving QoL or prolonging life in patients receiving palliative care input. These procedures should be carefully discussed with the patient and the person responsible, as well as health care professionals involved in their care

For information on procedures performed for palliative patients, including spinal decompression and/or fusion, ITDD systems, cordotomy, vertebroplasty/kyphoplasty, and neurolytic blocks, see Chapter 4, and previous sections of this chapter.

Commonly performed surgeries in patients receiving palliative care

Surgical xation of a pathological fracture

A pathological fracture is a fracture that develops through an area of bone pathology, typically either spontaneously or following minimal trauma

The goal of treatment is to minimize pain and maximize function. The nature of the surgical procedure is best determined by an experienced orthopaedic surgeon and may include arthroplasty or internal xation with intramedullary nailing or plate/screw xation devices

An impending fracture is where the extent of bone pathology is such that a fracture is expected but has not yet occurred. Prophylactic surgical xation may be considered for impending fractures

Radiotherapy should be considered following surgical xation of a pathological or impending pathological fracture or may occasionally be considered as primary treatment for an impending pathological fracture

Patients with pathological fractures may bene t from perioperative LA blocks or catheters as part of their multimodal analgesia, i.e. a fascia iliaca block/catheter for a neck of femur fracture or an interscalene block/catheter for a pathological fracture of the proximal humerus

Venting gastrostomy, defunctioning ileostomy, or colostomy formation

When a patient with metastatic cancer has an unresectable lesion or lesions causing multi-level bowel obstruction, a stoma may be created from the most proximal unobstructed segment of the GI tract to relieve the obstruction and associated nausea and vomiting. This may be an ileostomy or a colostomy

A venting gastrostomy allows a patient to drink and have a soft diet and then contents of the stomach are drained out via a gastrostomy tube. The person does not absorb nutrients but can retain the pleasure and social aspect of eating, with reduced nausea or vomiting

A person with a defunctioning ileostomy or colostomy may still e ectively absorb nutrients, depending on the length of the residual small bowel

Oesophageal, duodenal, colonic, or rectal stent

It may be possible to relieve a single-level obstruction due to malignancy with endoscopic stent insertion by a gastroenterologist or an upper GI or colorectal surgeon

Biliary stent

A biliary tree stent may be placed via endoscopic retrograde pancreaticocholangiography (ERCP) for malignant pancreaticobiliary obstruction

The most common complications are stent occlusion and stent migration

If it is not possible to relieve biliary obstruction via ERCP and stent insertion, it may be possible to relieve biliary obstruction with an external drain via percutaneous transhepatic cholangiography

Biliary decompression can relieve jaundice and pruritus and minimize the likelihood of cholangitis

Ureteric stent, percutaneous nephrostomy, or suprapubic catheter

Malignant obstruction to urine ow may occur at any level of the urinary tract

Ureteric obstruction may be relieved by insertion of a ureteric stent via cystoscopy or by surgical or interventional radiology placement of percutaneous nephrostomy

Ureteric stents and percutaneous nephrostomies may be performed unilaterally or bilaterally

Obstruction below the level of the bladder may be relieved by insertion of an indwelling urinary catheter or a suprapubic catheter

Post-procedure, one needs to diligently monitor and manage any post-obstructive diuresis

Airway stent

Airway stents are devices with a hollow lumen that are inserted into an airway bronchoscopically to relieve central airway obstruction

Further reading

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SECTION 7

PSYCHOLOGY OF PAIN MEDICINE

CHAPTER 30

Psychology and Pain



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30.1 Psychometric assessments

Definition

Chronic pain is often accompanied by symptoms of psychological distress and psychiatric disorders, including depression, anxiety, and anger

Psychometrics permit the quantification of cognition, affect, and behaviour, thus enabling the identification of both the pathology and the degree of deviation from normality

Psychometric assessment tools

Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)

A significant portion of patients presenting with chronic pain also have a history of primary psychiatric comorbidity

It is important to distinguish patients with an underlying psychiatric illness from those whose psychological symptoms (anxiety, depression, or other expressions of psychopathology) arise secondary to their pain

Beck Depression Inventory (BDI)

A brief, 21-item questionnaire that assesses the degree to which depressive symptomatology is present

Hospital Anxiety and Depression Scale (HADS)

A highly validated scale which consists of 14 items—seven for anxiety and seven for depression. Each item scores from 0 to 3 points

A total score of >8 out of 21 for anxiety and/or depression represents a clinically significant risk of these entities

General Health Questionnaire (GHQ)

A psychometric screening tool to identify common psychiatric conditions

There are versions with 12, 28, 30, and 60 questions, valid for use in adults and adolescents, but not in children; available free

Minnesota Multiphasic Personality Inventory-2 (MMPI-2)

An extensive true/false questionnaire consisting of >500 items factored across ten clinical scales, as well as a variety of validity, secondary, and experimental scales

The MMPI-2 has been used to verify clinical impressions about the psychological aspects of a patient's chronic pain and to predict responses to medical and surgical pain treatments

Pro le of Mood States (POMS)

A relatively new psychological rating scale used to assess transient, distinct mood states

Advantages of using this assessment include simplicity of administration and ease of participant's understanding

The POMS measures six di erent dimensions of mood swing, i.e. tension or anxiety, anger or hostility, vigor or activity, fatigue or inertia, depression or dejection, and confusion or bewilderment over a period of time

Patient Health Questionnaire-9 (PHQ-9)

Multipurpose instrument for screening, diagnosing, and monitoring of depression

It is brief, completed by the patient in minutes, and rapidly scored by the clinician

Generalized Anxiety Disorder-7 (GAD-7)

A questionnaire with seven items, which measure the severity of various signs of generalized anxiety disorder according to reported response categories with assigned points

The BDI, HADS, and GHQ can be used as self-report measures and all have standardized cut-o points that can be used to indicate a possible psychiatric state

Additional information

Given the multiple measurement scales used in clinical practice, the IMMPACT recommended **BDI** and **POMS** to be used as core outcome measures of emotional functioning in chronic pain clinical trials

They 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 chronic pain

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30.2 A ective component of pain

Introduction

Two components to pain:

- Sensory/discriminative
- A ective/emotional

The a ective component of pain is the emotional reaction and perceived sense of experience and is usually associated with some emotional distress

It varies in individuals, depending on certain factors, including:

- Situational context
- Pain characteristics and previous pain experiences
- Patient's understanding, family, and cultural background
- Coping responses

Stages

Immediate stage—unpleasantness/distress associated with intensity/arousal in the moment

Secondary stage—memories, imagination, prediction of long-term consequences

Common emotional reactions include anxiety, fear, frustration, anger, sadness, irritability, and depression

Assessment

Assessment of symptoms, such as fatigue, activity level, and sleep disturbance, may be di cult in chronic pain patients due to the impact of the a ective component

Such symptoms may be as a result of the pain, emotional distress, or medication/treatments

Multidimensional assessment necessary

Psychosocial evaluation

Comprehensive psychosocial evaluation should include:

Impact (physical, emotional, psychological, spiritual)

- Be aware of patients who may nd it di cult to label/communicate their a ective/emotional experience

Response to pain/coping skills (adaptive and maladaptive)

Avoidance (pain, stressors)

Meaning of the pain to the patient and previous experience of pain/treatment and expectations (of the patient, of others)

Medication and other health conditions (physical, psychological/psychiatric)

History of trauma/PTSD

Current support, contextual issues (additional stressors, family, social, work-related, bene ts, legal)

Assess for suicidal thoughts and intentions (follow local risk protocol/procedures)

Questionnaires

Self-reporting scales proposed to measure the a ective component:

- Pain Discomfort Scale
- VRS

Self-reporting measures, which capture aspects of the a ective component:

- *Anxietyanddepression:*
  - HADS
  - BDI
  - Beck Anxiety Inventory (BAI)
- *Stressandanxietysymptoms:*
  - Stress Symptoms Checklist (SSCL)
- *Cognition/beliefs:*
  - Pain Cognition Questionnaire

Coping:

Coping Strategies Questionnaire (CSQ)

Acceptance:

Chronic Pain Acceptance Questionnaire (CPAQ)

Moodandemotionalfunctioning:

POMS

Psychologicalfunctioning:

Symptom Checklist-90 Revised (SCL-90R)

Examples of self-report multi-dimensional measures, which include some measure of the a ective component:

McGill Pain Questionnaire (MPQ) (short-form MPQ-SF)—most widely used measure

Brief Pain Inventory (BPI)

Multi-dimensional Pain Inventory

Questionnaires recommended by IMMPACT in the United States:

Multi-dimensional Pain Inventory

BDI and/or POMS

Special points

Questionnaire scores should be interpreted with caution

Measures should be validated for chronic pain patients or criteria may require modi cation to avoid false positives

Should be relevant to the intervention

Speci c scales may be available for special populations, e.g. pain assessment checklist for seniors with severe dementia (PACSLAC)

Further reading

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30.3 Opioid risk assessment tools

Introduction

All patients who are to be commenced on opioids need to be assessed for characteristics that increase the likelihood of opioid abuse

Opioid risk assessment tools help in making this assessment

Tools

CAGE-AID (adapted to include drugs)

This screening tool has four questions. This is not speci c for opioids

Prescription Drug Use Questionnaire—patient version (PDUQp)

A validated, 31-item questionnaire for assessing and predicting problematic opioid medication use in chronic pain patients

Data are obtained regarding the patient's pain condition, opioid use, social and family history, and any psychiatric issues

Screening Instrument for Substance Abuse Potential (SISAP)

The SISAP is a 5-item screening tool that assesses the risk of opioid abuse, based on a patient's alcohol consumption, marijuana use, tobacco use, and age (non-validated)

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

A revised and validated version of the original self-report SOAPP to predict aberrant medication-related behaviours amongst chronic pain patients considered for long-term opioid therapy

It helps determine the level of monitoring required. This version contains 24 items and psychometric values

Opioid Risk Tool (ORT)

A validated 5-question tool to assess the risk of opioid abuse or aberrant behaviour

It helps determine the level of monitoring required by stratifying patients as low, medium, and high risk

Current Opioid Misuse Measure (COMM)

A highly sensitive and speci c, validated 17-question tool designed to identify aberrant drug-related behaviour (ADRB) during chronic opioid therapy

Severity of Opioid Dependence Questionnaire (SODQ)

This is a tool used as an indicator of opioid dependence

Three items are especially important in identifying opioid dependency: the tendency to increase the analgesic dose or frequency, the tendency to have a preferred route of administration, and the tendency to consider oneself addicted

Patient Medication Questionnaire (PMQ)

This is a validated 26-item questionnaire to assess ADRB in patients already on opioids (score <25: low risk of opioid abuse; 25–30: problematic use; >30: patient requires close monitoring and titration o opioids should be considered)

Additional points

None of the opioid risk assessment tools are perfect in predicting the risk of opioid abuse. They have to be used in conjunction with other methods of assessment, which include a thorough history, physical examination, and tests such as urine toxicology

SOAPP-R and ORT are the most accurate in predicting the risk of opioid abuse before starting therapy

PMQ and COMM are better at predicting ADRB once opioid therapy has been initiated

Risk assessment should be done before commencing opioid therapy and at regular intervals during therapy

Further reading

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30.4 Depression, anxiety, and suicidal ideation

Introduction

Mood disorders can be commonly associated with chronic pain

The most common symptoms are anxiety and depression

Changes in mood are as a result of the impact of chronic pain

Some patients may also have a premorbid psychological or psychiatric history

Depression—criteria

Psychological symptoms that have persisted for >2 weeks

Continuous low mood, irritability, intolerance (subjective report: feels sad/empty; observation: angry/tearful)

Feeling hopeless and helpless

Feeling guilty/worthless (guilt is usually inappropriate or excessive)

No motivation or interest in things

Di culty in decision-making (inability to concentrate/indecisiveness)

No enjoyment in life

Suicidality (having suicidal thoughts or thoughts of self-harm)

Anxiety—criteria

Fear and worry are normal emotions and can be appropriate emotions for those su ering from chronic pain

Clinical anxiety presents with the following symptoms:

- Excessive worry and feelings of apprehension (persistent for at least 6 months)
- Physical symptoms such as palpitations, sweating, and tension
- Symptoms cause signi cant distress or impairment in social, occupational, and other areas of functioning
- Symptoms are not related to physiological substances, such as medications and drug abuse, or a medical condition such as heart problems and hyperthyroidism

Suicidality

Substantially increased risk of suicide in those living with chronic pain

Main predictors are negative pain-coping strategies and the degree of pain-related catastrophizing

Suicidal ideation may be active or passive:

- Passive: involves a desire to die, but without a speci c plan of how the patient might end their life
- Active: involves a wish to die accompanied by a plan of how they intend to end their life

Parasuicide is an attempt at suicide where the aim is to deliberately fail and the person puts in plans to be discovered

Co-occurring disorders should also be noted, as sometimes suicidal ideation could be a symptom of diagnosed or undiagnosed mental health

Patients may use catastrophic terms, 'I would be better o dead'—this may not mean they intend to end their life but nonetheless should be followed up with questions about intent

Assessment

Clinical interview to include risk assessment of suicidal intent

Questionnaires

GAD-7—this may be used as a screening tool to measure levels of anxiety

Patient Health Questionnaire-2 (PHQ-2) may be used in screening for depression, and PHQ-9 for monitoring depression

Refer to DSM-IV, which can be found online

Treatment/referral

Give an explanation to the patient of how mood impacts on pain, and vice versa, causing a circular e ect

Mood disorders related to psychosocial symptoms—referral for **counselling**

Mild anxiety and depression—referral for Improving Access to Psychological Therapies (**IAPT**)

Moderate anxiety and depression—referral for **CBT**

Severe anxiety and depression a ective of pain symptoms—referral to specialist pain/**physical health psychology** services

Severe anxiety and depression not related to pain symptoms—referral to adult mental health team (**AMHT**)

Passive suicidal ideation—mood must be monitored

Active suicidal ideation—referral to **mental health crisis team** and psychiatry

Further reading

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30.5 Fear avoidance behaviour, catastrophizing, and pain behaviours

Fear avoidance behaviour

The fear avoidance model uses a cognitive behavioural model

Components include pain experience, catastrophizing, fear of pain, avoidance/escape, disuse, and disability/depression

Chronic MSK pain is developed as a result of avoidant behaviour

Pain is initially experienced; the patient then engages in avoidant behaviour (e.g. restricting movement, not bending/carrying) as a result of fear of pain

Resulting lack of pain reinforces the avoidant behaviours, which leads to deconditioning/further pain

Hypervigilance to pain/discomfort and avoidant behaviours lead to a vicious cycle

Experience/anticipation of further pain reinforces avoidant behaviours and fears, exacerbating hypervigilance to pain/discomfort

Misdirected problem-solving—pain is perceived to cause damage, leading to behavioural priority of escape/avoidance and increased vigilance for pain

In uenced by characteristics of the pain (bottom–up processing) and cognitive and emotional appraisals/experiences/memories/expectations (top–down processing)

Associated with poorer outcomes for employment, inactivity, greater disability/impaired physical performance, increased pain, catastrophizing, anxiety, and depression

Fear Avoidance Beliefs Questionnaire (FABQ) is helpful in understanding the patient's beliefs

To address fear avoidance

Reinstate normal activity levels

Fear hierarchy—graded exposure

Pacing activity

Change perceptions of pain (i.e. non-threatening/temporary)

Catastrophizing

Cognitive process characterized by:

- Interpretation of negative events as being more negative than they really are
- Perceiving events/sensations as 'out of proportion'
- Overestimating the probability of negative events occurring
- Excessive/exaggerated negative self-statements

Pain is perceived as being 'extremely threatening'

Associated with

Fear avoidance behaviour

Low frustration tolerance and high levels of psychological/emotional distress

Activity intolerance/lower levels of activity

Intensi ed experience of pain

Pain disability and related fear

Negative control beliefs and coping outcomes

Perceptions of poor self-e cacy
Depression
Higher rates of analgesic use
The **Pain Catastrophizing Scale (PCS)** measures pain-related catastrophic thoughts.

Pain behaviours

Expression of distress—verbalizing, crying, groaning, grimacing
Changes to movement—guarding, limping, bracing, rubbing body parts
Changes to posture—tense, rigid, slouching, bending
Avoidance of activity
Other pain behaviours—medication/alcohol/drug use, treatment seeking

Pain behaviours may be

Learnt responses to pain/habit in an attempt to reduce pain and distress and seek help and support
Indication of exaggeration/faking
Associated with excessive concern from others (particularly partners)

Managing pain behaviours

Make conscious, if unaware, and explore reinforcers
Assertiveness skills
Set clear goals
Teach adaptive behaviours
Explore others' responses to pain (family, professionals)

Treatment

Fear avoidance behaviour, catastrophizing, and pain behaviours are ameliorable to CBT and ACT
Behavioural aspects of the therapies focus upon fear exposure and building skills in more helpful behavioural strategies for pain management and expression of distress
Cognitive aspects of the therapies focus upon reducing the belief that the pain requires medical intervention, shifting focus from cure to management of the pain by the individual

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30.6 Personality disorders

Introduction

A person with a PD may have limited ways of feeling, behaving, or thinking

Impacts upon relationships, interactions with others, and coping and life skills

People with a PD generally feel isolated and have a higher risk of suicide and higher levels of self-harm and addictive tendencies

PDs can typically coexist with other mental health conditions (depression, bipolar disorder, substance abuse, eating disorder, anxiety disorders)

No clear de nition of why people develop PD

Research suggests several causal factors that tend to be grouped into internal, genetic, and external factors (victims of abuse, childhood neglect, childhood trauma, chaotic family life, parental alcohol/drug abuse, parental mental health)

Research carried out in 2006 suggests that approximately one in 20 people will have a PD at any given time

De nition

Ten speci c PDs, placed into three clusters, as identi ed in DSM-5 (see Table 30.6.1)

Table 30.6.1 Personality disorders

Clusters1	Key attributes
Cluster A—suspicious	Paranoid (distrust others, suspicious and guarded, very sensitive, have di culty maintaining close relationships) Schizoid (behave introvertedly, emotionally cold, indi erent, little pleasure in life) Schizotypal (odd/eccentric behaviour, believe they can read minds and have special power, prone to developing schizophrenia)
Cluster B—emotional and impulsive	Antisocial (disregard for others, impulsive, aggressive, prioritize their needs) Borderline (lack sense of self, fear of being abandoned, di culty in controlling anger/maintaining relationships, increased suicidal thoughts, prone to developing paranoia) Histrionic (lack self-worth, attention-seeking behaviour, in uenced by others) Narcissistic (entitled, self-absorbed behaviour, controlling, lack empathy, constant need to be admired)
Cluster C—anxious	Avoidant (feel socially inept and inferior, isolated and lonely, avoid interactions with others and relationships, fear of rejection) Dependent (feel helpless and lack self-con dence, cannot make independent decisions, passive and submissive, fear of being abandoned) Obsessive–compulsive* (perfectionism, in exible, set unrealistic high standards for all and self, preoccupied with orderliness and control, fear of making mistakes)

*Obsessive– compulsivepersonalitydisorder(OCPD)isseparatefromobsessive– compulsivedisorder(OCD).OCDis ananxietydisorder,notatypeofpersonalitydisorder.

Source:DatafromAmericanPsychiatricAssociation.(2013). *Diagnosticandstatisticalmanualof mentaldisorders:DSM-* 5. Arlington,VA:AmericanPsychiatricAssociation.

Treatment

Complex nature of PD makes treatment very challenging

Previously thought to be 'untreatable' and a 'diagnosis of exclusion' from services

People with PD tend to find it difficult to engage in therapy and often drop out of therapy due to:

- Self-damaging behaviours
- Inability to form relationships (including therapeutic relationships)

Specialist treatment is required:

- Dialectical behaviour therapy (DBT) is a cognitive behavioural treatment developed to specifically treat people who experience intense emotions
- Therapeutic communities (TCs) are structured environments for people with complex psychological conditions

Referral (useful websites for NHS referral)

http://www.nhs.uk/Conditions/Borderline-personality-disorder/Pages/Treatment.aspx

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30.7 Somatic symptom disorder

Introduction

Somatic symptom disorder (SSD), previously referred to as somatization disorder

The diagnostic class for SSD emphasizes distressing somatic symptoms with extreme reactions and behaviour and distress towards the symptoms, rather than the absence of a medical explanation for somatic symptoms

Prevalence of SSD is 5–7% in the general population, and higher in neurology settings (25%)

Criteria

The patient presents with extreme anxiety about physical symptoms

The diagnostic criteria for SSD are summarized from DSM-5:

- One or more somatic symptoms that cause major distress and result in significant disruption of daily life

Excessive thoughts, feelings, or behaviours related to symptoms or associated health concerns, as evident by at least one of the following:

1. Disproportionate and persistent thoughts about the seriousness of one's symptoms
2. Persistently high level of anxiety about health or symptoms
3. Excessive time and energy devoted to these symptoms or health concerns[1]

Although any one somatic symptom may not be continuously present, the state of being symptomatic is generally persistent for >6 months

Severity:

Mild—only one of symptoms (1) to (3) are speci ed

Moderate—two or more of symptoms (1) to (3) are speci ed

Severe—two or more of symptoms (1) to (3) are speci ed plus there are multiple somatic complaints or one very severe somatic symptom

Generally dominant symptoms are somatic complaints, health anxiety, and pain

Sexual abuse has also been associated with an increased risk of SSD

Associated comorbidities include depression, IBS, and PTSD

Treatment—psychological therapy

CBT

Mindfulness

The main aim is to empower and help the patient cope with the symptoms

Special notes

After appropriate diagnostic tests are performed, a consultation explaining and describing the condition must be carried out with caution and without implication of a psychosomatic illness

A patient with SSD is not purposely faking their symptoms—the pain they feel is real

Patients will bene t from support within a trusting relationship, as this will help avoid unnecessary future investigations, while enabling observation of symptoms that may require investigation

Referral

A psychiatric referral may be bene cial

However, CBT has been shown to be more e ective than psychiatric intervention

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30.8 Post-traumatic stress disorder

Introduction

PTSD is a chronic and debilitating condition that can develop in response to a traumatic life event or events

Symptoms of PTSD are divided into three clusters:

- Re-experiencing
- Avoidance
- Hyperarousal

Other symptoms include feelings of guilt, dissociation, alterations in personality, di culty with a ect regulation, and marked impairment in ability for intimacy and attachment

Comorbid disorders include severe anxiety, depression, dissociative disorder, substance abuse, suicidal feelings, and a range of physical complaints

De nition

Trauma is de ned when:

- A person experiences, witnesses, or has been confronted with an event or events that involved actual or threatened death or serious injury or a threat to the physical integrity of self or others
- The person's response involves intense fear, helplessness, or horror

Can occur following a single traumatic incident or can be related to a series of events/prolonged event (complex PTSD)

Assessment

Referral to a mental health professional for assessment if symptoms have persisted for longer than 4 weeks

Questionnaires

Clinician-Administered PTSD Scale (CAPS)

The Impact of Event Scale–Revised (IES-R)

Treatment

Watchful waiting—monitoring in initial stages (symptoms for <4 weeks); two in three people show spontaneous improvement

Antidepressants (paroxetine and sertraline are licensed for PTSD)

Eye movement desensitization and reprocessing (EMDR)

Trauma-focused cognitive behavioural therapy (TF-CBT)

Specialist services, depending on nature of trauma (Combat Stress, Rape Crisis, etc.)

Further reading

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30.9 Compensation issues

Suggestions are that financial compensation influences pain and treatment outcome via secondary gain, reward for the learnt pain behaviour, malingering, and compensation neurosis.

Primary and secondary gain

Gains derived from the illness/symptom, which may act as a maintaining factor

Primary gain

Subconscious internal psychological motivators for symptom presentation
Produces positive internal motivation
Reduction of internal distress/emotional conflict/anxiety as a result of the symptom/illness

Secondary gain

Subconscious or conscious external motivator
Interpersonal or social advantage
Examples: increased care, disability benefits, reduction of responsibilities, etc.

Malingering

Symptoms fabricated/exaggerated for secondary gain
Rare
DSM-IV diagnosis

Fictitious disorder

Symptoms fabricated/exaggerated for primary gain

Compensation neurosis

Compensation being sought for an injury/condition
Financial compensation identified as the primary maintaining factor for symptoms
Symptoms resolve on settlement
Theory not supported by research evidence

Experience of pain and compensation

Limited evidence that receiving financial compensation is associated with a greater experience of pain/disability
Limited evidence to support that those going through litigation exaggerate pain

Some evidence of worse prognosis for those who have received compensation, di cult to specify causal factors

Likely to be related to type of treatment/rehabilitation programme and nature of injury

Treatment outcome and compensation

Perception that nancial compensation has a negative e ect on rehabilitation/treatment outcome

Controversial, con icting evidence

Studies awed (di ering outcome measures, patients' conditions not comparable, types of compensation, disability not accounted for)

Meta-analysis suggests no clear conclusion

Associated issues related to compensation and experience of pain/ treatment outcome

Fears of nancial di culty

Job satisfaction

Anger at those perceived to be responsible for injury

Lack of support/adaptations at work

Employment status

Trauma and PTSD

Severity of pain

Disability

Levels of emotional distress

Impact on life

Further reading

1. Rohling ML, Binder LM, Langhinrichsen-Rohling J. Money matters: a meta-analytic review of the association between nancial compensation and the experience and treatment of chronic pain. Health 1996;14(6):537–47
2. Turk DC, Okifuji A. Perception of traumatic onset, compensation status, and physical ndings: impact on pain severity, emotional distress, and disability in chronic pain patients. J Behav Med 1996;19(5):435–53

30.10 Cognitive behavioural therapy

Introduction

Cognitions, emotions, physical sensations, and behaviours are linked

Cognitive appraisals determine emotions and behaviours, the consequences of which reinforce thoughts/beliefs

Patients identify how their thoughts, emotions, behaviours, and experience of pain are linked in maladaptive ways

Patients are taught coping skills to modify these maladaptive responses

Present focused and problem-speci c approach

Aims of therapy

Identify negative or maladaptive thoughts and behaviours
Change these in order to improve physical sensations and emotional experience

Theoretical background/proposed mechanisms

Increase in more adaptive cognitions via

Restructuring of maladaptive thoughts/beliefs
Changes in attention focus (away from the pain)
Development of more adaptive thoughts/beliefs

Increase in more adaptive behaviours via

Habituation
Extinction of maladaptive behaviours
Behavioural activation
Associative learning
Reinforcement of more adaptive behaviours

Decrease in physiological arousal via

Habituation
Incompatible response training
Changes in autonomic nervous system activity

Indications

Chronic pain
Insomnia
Psychological disorders, including:
- Anxiety disorders (panic disorder, agoraphobia, social phobia, speci c phobia, and generalized anxiety disorder)
- Depression
- OCD
- PTSD
- Eating disorders

Substance misuse
Also indicated for chronic pain and other medical conditions in children and adolescents

Contraindications

Patients with impaired cognitive functioning
Patients who are actively psychotic or intoxicated
Patients requiring emergency medical treatment
Patients seeking a cure for pain
Comorbid severe mood disorder may require medication, in addition to psychological therapy
Patients should be on a stable dose if taking any antidepressants, mood stabilizers, or antipsychotic medication
Actively suicidal patients should be monitored, and risk protocols adhered to

Complications/adverse e ects

Some emotional distress/anger, with exploration of di cult feelings/challenging beliefs
Temporary increase in anxiety with exposure

Technique

Implementation of CBT

Individually or in groups
Couples/family sessions
Pain management programmes
Self-help resources, computerized CBT
Sessions are goal-oriented and structured with an agreed agenda
Therapy is time-limited
Typically, 10–20 sessions, approximately 1 hour, once per week
May require additional sessions in more complex cases

Therapeutic strategies

Psychoeducation: to aid in the patient's understanding of chronic pain and adaptive strategies, to provide treatment rationale, and to introduce to CBT model
Cognitive restructuring: to identify maladaptive thoughts/beliefs, to challenge these, and to enable the patient to produce more adaptive thoughts/beliefs
Skills training:
- Goal setting
- Problem-solving
- Attention diversion/distraction
- Relaxation training
- Behavioural techniques to reduce pain behaviours and increase adaptive behaviours (e.g. pacing)
- Behavioural activation: to increase activities which provide pleasure/sense of mastery/achievement
- Relapse prevention: to prepare for, and normalize setbacks, plans for coping with future pain/stressors

Graded exposure: to reduce avoidance (of pain/stressors) and increase approach behaviour
Homework: agreed tasks between sessions to facilitate the above and to practise adaptive coping skills

Common CBT goals

Improvement of physical tness/stamina
Improvement of social skills, e.g. assertiveness
Improvement of pain-coping skills, e.g. pacing

Special points

CBT strategies should be modi ed/adapted for speci c populations (e.g. older adults) to meet their individual needs

E ectiveness

CBT is the most comprehensively researched psychotherapeutic treatment for pain
Good evidence to support the use of CBT in chronic pain
Level of evidence: 1+

Further reading

1. Butler AC, Chapman JE, Forman EM, et al. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev 2006;26(1):17–31
2. Eccleston C, Palermo TM, Williams AC, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2014;5:CD003968
3. Williams, A, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2012;11:CD007407

30.11 Acceptance and commitment therapy

Introduction

Third-wave CBT

Acceptance that pain is an inevitable part of life

Su ering is caused by the response to pain, rather than the pain itself

Su ering = resistance + pain

Attempts to 'escape the pain' results in more su ering

Aim of therapy—pain acceptance

To be willing to experience pain

To engage in valued life activities, despite pain

Theoretical background/mechanisms

Patient learns to observe the pain and their attempts to escape/avoid it

Increased awareness of this process allows increased choice of avoidance or exposure behaviours

Indications

Any issue where the only adaptive strategy is acceptance, e.g. chronic pain, childhood trauma

Comorbid presentations may bene t from intensive ACT

Contraindications

Patients with impaired cognitive functioning

Patients who are actively psychotic or intoxicated

Patients requiring emergency medical treatment

Patients should be on a stable dose if taking any antidepressant, mood stabilizer, or antipsychotic medication

Antisocial behaviours that can be controlled, e.g. aggression, criminal activity

Actively suicidal patients should be monitored, and risk protocols adhered to

Complications/adverse reactions

Some emotional distress/anger with exploration of di cult feelings/challenging beliefs

Temporary increase in anxiety with exposure

Table 30.11.1 The Hexa ex

Mindfulness and acceptance processes	Commitment and behavioural change processes
1. Acceptance (of thoughts/sensations/urges)—reduction of maladaptive attempts to avoid pain 2. Defusion (observe thoughts without believing/acting upon them)—less investment in pain-related thinking 3. The observing self—increases present-moment self-awareness	4. Being present—focus on present moment despite pain 5. Values—identi cation of personal values and engagement value-related activities despite pain 6. Committed action—engagement in more helpful pain-coping strategies

Technique

ACT can be implemented as individual therapy, couples therapy, group therapy, part of MDT pain management programmes, or self-help resources

Can be delivered as brief (1–4 sessions), intensive, or longer term (10+ sessions) therapy

Building skills/psychological exibility in the six core processes shown in Table 30.11.1)

Outcome measured with the CPAQ

Special points

'Clean pain' (unconditioned pain) is the experience of pain (sensory and a ective)

'Dirty pain' (conditioned pain) is the associated response to the experience of pain—thoughts/judgements/expectations/beliefs, resistance to pain/emotional experience

E ectiveness

Strong research base for ACT in chronic pain

E ective within MDT, in both outpatient and residential programmes

Acceptance of pain has been correlated with lower pain intensity, less pain avoidance, increased physical and social ability, improved work status, and less associated depression and anxiety

Level of evidence: 1+

Further reading

1. Dahl J, Wilson K, Nilsson A. Acceptance and commitment therapy and the treatment of persons at risk for long-term disability resulting from stress and pain symptoms: a randomized control clinical trial. Behavior Therapy 2004;35:785–802
2. Eccelstone C. Psychology of chronic pain and evidence-based psychological interventions. In: Stannard CF, Kalso E, Ballantyne J (eds). Evidence-based Chronic Pain Management. 2010; pp. 59–67. Oxford: BMJ Books
3. McCracken LM, Vowles KE, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. Pain 2004;107:159–66

30.12 Mindfulness

Introduction

Mindfulness-based approaches involve **meditation** and a way of living **focused upon present-moment** awareness, acceptance, and compassion

- Develop attentional skills and acceptance
- Reduce pain-related arousal and reactivity

Focus upon accepting all experiences (neutral, unpleasant, or pleasant) to enable a choice of response to the pain

Aim

To develop an accepting and kind relationship with the pain (primary su ering) in order to reduce secondary su ering (maladaptive reactions to the pain), and thereby improve QoL

Theoretical background/proposed mechanism

To cultivate an attitude of acceptance/recognize the nature of experience as transient (reduction of hypervigilance and emotional reactivity, extinction through counter-conditioning)

Distraction technique—shifts attention from pain

Exposure to pain—habituation

Higher activation levels in areas of the brain implicated in attention, cognitive control, somatic awareness, and stress regulation in pain-related regions (dorsal anterior cingulate cortex, insula, and thalamus)

Lower activation in areas involved in appraisal, emotional regulation, stress, and memory (medial prefrontal cortex, orbitofrontal cortex, amygdala, and DLPFC)

Indications

Chronic pain, chronic illness

Stress and psychological distress

Psychological disorders, including anxiety, depression, and OCD

Contraindications

Dissociative tendencies/disorders, suicidal ideation

Active addiction or <1-year recovery

Psychosis, PTSD

Patients who nd it di cult to 'sit with' discomfort (physical, emotional, cognitive), those who habitually use avoidant coping strategies

Complications/adverse e ects

Rare cases of depersonalization, psychosis, increased anxiety and risk of seizures, loss of appetite, and insomnia have been reported

Such adverse e ects are more likely to occur with prolonged meditation

Technique

Individually or in groups

Patients are taught meditative practices to increase present-moment meta-awareness and to develop an accepting, non-judgemental, and kind attitude to all experiences (physical, emotional, and cognitive)

Patients are encouraged to develop their own daily meditative practice

Special points

Often included as a skill taught within psychological therapies such as mindfulness-based stress reduction (MBSR), mindfulness-based CBT (MCBT), ACT, and DBT

The focus of mindfulness is not upon attempting to ignore/escape pain, but rather on cultivating an attitude of acceptance of it, thereby reducing secondary distress

Although linked to certain religious philosophies in clinical practice, mindfulness is taught in a secular way

E ectiveness

Reports suggest it can be a good alternative to CBT

Growing evidence base

Level of evidence 2++

Further reading

1. Carmody J, Baer RA. Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and wellbeing in a mindfulness-based stress reduction program. J Behav Med 2008;31(1):23–33
2. Zeidan F, Grant J, Brown CA, et al. Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain. Neurosci Lett 2012;520:165–73

30.13 Hypnotic therapy

Introduction

Altered state of conscious awareness

Patient becomes more open to 'suggestions', which can create changes in perception and behaviour

Can be used alone or to enhance the e ectiveness of other interventions

Can develop skills in auto-hypnosis

Hypnotizability is dependent on:

Motivation and beliefs

Ability to achieve a state of hypnosis and experience a range of hypnotic phenomena

Ability to learn/use self-hypnosis

Being receptive/responsive to hypnotic suggestion

Theoretical background or proposed mechanisms

Reduction of anxiety, increased relaxation

Altered perception (reduction in hypervigilance for pain)

Modi cation of maladaptive cognitions regarding pain

Less dissonance in response to ideas/suggestions contrary to patient's maladaptive beliefs

Information processing enhanced due to reduced preoccupation with pain

Reduction of cortical activation associated with painful stimuli

Indications

Post-operative pain

Cancer pain

IBS
Labour pain
Headaches
Dental procedures
Neuropathic pain
MSK pain

Contraindications

Patients with impaired cognitive functioning
Patients who are intoxicated
Patients requiring emergency medical treatment
Psychosis, severe mood disorder, dissociative disorders, suicidal ideation
Epilepsy, narcolepsy
High/low BP and serious heart conditions
Controversy over whether it should be provided in pregnancy (except during labour)

Complications/adverse e ects

Rare but can include headache, tiredness, anxiety, confusion, creation of false memories, and panic attacks

Technique

Orient patient to hypnosis; assess beliefs related to hypnosis and hypnotizability
Patient induced into a relaxed hypnotic state by practitioner using words and imagery
Practitioner provides suggestions to modify patient's pain-related thoughts/images
Build an adaptive repertoire of thoughts/images associated with pain relief
Debrief patient and check for amnesia
Set individual self-hypnosis exercise

Hypnobehavioural strategies

Imagery and controlled breathing
Relaxation, distraction
Mental rehearsal of adaptive pain-coping behaviours
Cognitive restructuring (via age regression, memory recall, memory reconstruction, positive self-suggestion, altering negative thoughts)
Strategies for altering pain sensations (e.g. distraction, pain displacement, symptom substitution, hypno-analgesia, glove analgesia/anaesthesia, symptom reinterpretation/reframing, time distortion, pain relief imagery)

Special points

Cannot hypnotize someone against their will
One of the rst mind–body approaches used for chronic pain
Hypnotic state is di cult to measure objectively
In research on e cacy, hypnosis may be viewed within the cognitive behavioural model rather than the hypnotic state theory
Hypno-behavioural pain management psychotherapy
Patients rated by practitioners as having 'high hypnotizability' report greater bene ts from hypnosis

E ectiveness

Established e cacy for chronic pain

Hypnosis may help relieve pain in labour, but research conducted so far has not conclusively shown bene t

Level of evidence: 1

Further reading

1. lkins G, Johnson A, Fisher W. Cognitive hypnotherapy for pain management. Am J Clin Hypn 2012;54(4):294–310
2. Madden K, Middleton P, Cyna AM, Matthewson M, Jones L. Hypnosis for pain management during labour and childbirth. Cochrane Database Syst Rev 2012;11:CD009356

30.14 Neurolinguistic programming

Introduction

Neurolinguistic programming (NLP) is a coaching method

Often used in personal development and corporate settings

It claims the following:

- Individuals have unique internal mental maps
- Connection between neurological processes and language and behavioural patterns learnt through experience (programming)
- To achieve speci c goals, these connections can be changed
- Through 'modelling' skills of successful/exceptional people

Seen as a pseudoscience, largely discredited scienti cally

Aim of therapy

To change conscious and subconscious beliefs about themselves, the pain/illness, and the world

Mechanism

Uses techniques from hypnotherapy and psychotherapy

Reports to 'reprogramme' limiting beliefs

Behaviour modi ed through manipulating 'subjective representations' we hold about ourselves/the world

Change internal representations and responses to stimuli in the world

Enables patients to make adaptive lifestyle changes using an imitative method of learning (modelling)

Placebo e ect?

Indications

Changing behavioural patterns

Stress reduction

Fears and phobia

Coaching, personal performance

Contraindications

Bipolar disorder, PDs, attachment and impulse control disorders
Patients in recovery from substance misuse
Patients with cognitive impairment
Patients who struggle to understand/apply metaphors

Complications/adverse e ects

Often reported by practitioners as having no adverse e ects
However, some reports of adverse e ects on mental health/well-being

Technique

Can be implemented individually, in seminars, and as self-help resources
Practitioners claim that problems can be 'reprogrammed' quickly, in some cases within <1 hour
Identify negative attitudes and beliefs which have been 'programmed since birth'
'Reprogramme' beliefs via a wide variety of techniques, including:
- Visualization/imagery
- Mental rehearsal

NLP for pain is useful when patients treat pain as a phobia. It helps increase self-e cacy and visualization, redirecting focus away from pain and 'remapping' beliefs

Special points

Medical and psychological practitioners may employ aspects of NLP; however, it is **not** mainstream medical/psychological practice
The eld of NLP is self-regulated

E ectiveness

There is limited evidence on the e ectiveness of NLP in chronic pain
Level of evidence: 3 and 4

Further reading

1. Bowers, L.A. An exploration of holistic and non-traditional methods including research in the use of neuro-linguistic programming in the adjunctive treatment of acute pain. Dissertation Abstracts International 1996;56(11-B):6379

30.15 Pain management programmes

Introduction

Pain management programmes (PMPs) are an established part of care for patients su ering from chronic pain
PMPs are one of the most important non-pharmacological ways of helping patients with chronic pain manage their condition

They improve patients' understanding of chronic pain through a combination of psychological techniques and practical strategies designed to optimize physical functioning and QoL, and reduce emotional distress

Aims of PMPs

To improve the patient's understanding of chronic pain

To minimize the impact of pain on their everyday lives

To optimize physical functioning and QoL

To reduce emotional distress

To promote a self-management approach to pain

To provide coping skills and strategies for dealing with chronic pain, disability, distress, and life changes

To reduce or modify the patient's future use of health care services

To decrease the patient's reliance on medical management

Rationale for PMPs

Based on the biopsychosocial approach to pain

Addresses psychological and socio-cultural factors, in addition to biomedical/physiological aspects

Takes into account the multi-dimensional nature of pain and the interplay of psychological and psychosocial factors

Pain is in uenced by not only its underlying pathophysiology, but also by the individual's cognitions and behaviour:

- Psychological factors, such as mood, beliefs about pain, and coping style, play an important role in an individual's adjustment to living with chronic pain
- Persistent pain can lead to unhelpful behaviours (over-dependency on family, friends, and the medical profession, avoidance of regular activities, e.g. work, social activities, hobbies), and negative beliefs about their experience of pain and negative thoughts about themselves
- Negative cognitions, along with decreased activity, can then lead to depression and/or anxiety

Inclusion criteria

Have had pain for >6 months. Pain is persistent, disabling, and unresponsive to other therapies

Pain is causing signi cant disability/distress (e.g. widespread disruption of activity, habitual over-/underactivity leading to increased pain, poor progress in rehabilitation due to pain, high a ective distress or clear signs or reports of emotional distress, high levels of reported or observed pain behaviour (guarding, fear avoidance, catastrophizing)

The individual is receptive to adopting a self-management approach and is willing to participate in a group

Exclusion criteria

Limited life expectancy/rapidly deteriorating disease/condition

Suitable for further medical treatment

Certain psychiatric problems that would interfere with group management

Does not wish to take part in a group-based intervention for pain
Unable to commit to a PMP

Method of PMPs

Most PMPs apply a cognitive behavioural approach, a process of reconceptualization that maladaptive beliefs about the cause of pain can be modi ed
PMPs with a cognitive behavioural approach can be delivered using the following therapeutic models:
- CBT
- ACT

Other models are sometimes employed such as MBSR and compassion focused therapy (CFT)
Graded activity which is guided by the individual in the form of goal setting
Plan and practise activities to decrease fear and improve the ability to experience fear by a graded exposure technique
Group format, usually between eight and 12 individuals
Interdisciplinary team which can include medical sta , specialist nurses, physiotherapists, psychologists, occupational therapists, pharmacists, and past participants
Recommended duration should be the equivalent of 12 half-day sessions (some patients may bene t from more intensive programmes, e.g. 15–20 full days)

Contents of PMPs

Education on the nature, mechanisms, and factors in uencing chronic pain
Physical exercise
Identifying and challenging unhelpful beliefs about pain
Graded activation towards individual goals
Graded exposure to perceived threatening situations to reduce avoidance
Methods to enhance acceptance, mindfulness, and psychological exibility
Skills training and activity management (pacing, assertiveness, goal setting, managing setbacks/ are-ups, sleep)

Outcome measures

Changes in function
Psychological well-being
Pain experience
Health care use
QoL
Work status (where relevant)
Social activities and social role performance

E ectiveness

E ective in producing reduction in pain, improved mood, psychological coping, physical tness, pain communication and behaviour, and social role functioning
High level of evidence for interdisciplinary PMPs based on cognitive behavioural principles
Level of evidence: 1++

Special points

Introducing a self-management approach to patients can be very challenging as it is not a 'medical treatment'

Patients' suitability for PMPs is an important factor for outcome. Suitability is based on the impact of pain

Individual psychological and physiotherapy may also be required before, during, or after PMP

Further reading

1. The British Pain Society. Guidelines for pain management programmes for adults. 2013. https://www.britishpainsociety.org/static/uploads/resources/ les/pmp2013_main_FINAL_v6.pdf
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3. Royal College of Anaesthetists. Core standards for pain management services in the UK. Chapter 7, Section 7, 2015; pp. 119–35. London: Intercollegiate Colleges. https://fpm.ac.uk/sites/fpm/ les/documents/2019-07/Core%20Standards%20for%20Pain%20Management%20Services.pdf
4. LeMarchand K, Raphael JH. An open prospective study of coping factor dimensions and psychophysical health in patients undergoing a cognitive-behavioural group pain management programme for chronic pain. J Pain 2008;1:pp. 307–16
5. Scottish Intercollegiate Guidelines Network. Management of chronic pain: a national clinical guideline. 2013. https://www.sign.ac.uk/assets/sign136.pdf

SECTION 8

PHYSIOTHERAPY AND OCCUPATIONAL THERAPY

CHAPTER 31

Physiotherapy and Occupational Therapy

Rebecca Elijah-Smith and Fiona Thomas

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31.1 Principles of physiotherapy

De nition based on the Chartered Society of Physiotherapy

The physiotherapist uses exercise, manual therapy, education, and advice in order to help their patients restore movement and function when they are a ected by an injury, illness, or disability

The physiotherapist also helps to encourage development and facilitate recovery, enabling people to stay in work and helping them to remain independent for as long as possible

They also help to maintain health for the wider population, including assisting their patients to manage pain and prevent disease

Role of physiotherapy

Physiotherapists use their knowledge and skills to help treat a variety of conditions:

Neurological (e.g. post-stroke rehabilitation, MS, Parkinson's disease)

Musculoskeletal or MSK (e.g. back pain, whiplash-associated disorder, sports injuries, OA)

Cardiovascular (e.g. chronic heart disease, rehabilitation after MI)

Respiratory (e.g. asthma, COPD, cystic brosis)

Role of musculoskeletal physiotherapists

MSK physiotherapy can help with acute injuries such as sport injuries or whiplash. Physiotherapy can also help with the management of long-term conditions such as persistent lower back pain and Fibromyalgia Syndrome (FMS)

An essential element in the rehabilitation of a patient is self-management. This is the patient's involvement in their own care through education, awareness, empowerment, and participation in their treatment

Physiotherapy is an evidence-based profession and takes a holistic approach to health care

Musculoskeletal physiotherapy for chronic pain

Over the past few years, physiotherapists have started to use psychological principles in the management of their patients with long-term pain

More recent studies have also advocated the development of psychological skills within physiotherapy, and the term psychologically informed physiotherapists (PIPs) has now been widely adopted

Studies include the STarT Back tool which enables the primary care clinician to stratify the management of their patient according to patient prognosis (low, medium, or high risk) and targets treatment accordingly

The Back Skills Training Trial focuses on the management of chronic lower back pain using a cognitive behavioural intervention through a structured group-based programme

Skills of the chronic pain musculoskeletal physiotherapist

The physiotherapist is a core member of the interdisciplinary team and this role continues to develop

The pain physiotherapist or PIP will develop skills, which include:

- Cognitive behavioural theoretical principles
- Educational and teaching skills in order to be able to deliver appropriate information to a group of patients, but also to be able to educate their pain management colleagues in the area of physiotherapy management
- Facilitating a team approach, including interdisciplinary teamworking

In addition, the pain physiotherapist brings a variety of important skills to the pain team. These include manual therapy, electrotherapy, acupuncture, and therapeutic exercise knowledge

The physiotherapist will be able to integrate these skills into treatments, such as individualized sessions or Self Management Programmes (SMP's), using cognitive behavioural principles

E ectiveness

Level of evidence: 1A

There is a recognized need for continuous research

Further reading

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31.2 Principals of occupational therapy

Introduction

Occupational therapy promotes the health and well-being of people through occupational participation and engagement

Occupational therapists apply a client-centred, ecological approach to pain management, focusing on an individual's engagement in their daily life tasks

Occupational therapists support clients over the age spectrum and across di erent clinical services such as acute care, rehabilitation, community, mental health, case management, and health promotion

Roleof the occupational therapist in pain management

Intervention has a strong emphasis on self-management and functional engagement

Provides pain management as part of a multidisciplinary team for patients with acute, chronic and cancer pain and when pain coexists with other comorbidities such as SCI, amputation, stroke, and mental health issues

Assists individuals in identifying and addressing factors that limit their performance of self-care, productive roles, and leisure tasks. These factors may be a combination of individual, environmental, and/or people surrounding them

Skilled in understanding the challenges that clients face on a daily basis, and the in uence that the environment and social milieu have in supporting or hindering the client's ability to engage in meaningful activities

Occupational therapy assessment

Assessing the person's functional life and how pain has impacted ADLs, rest, productivity, and leisure

Utilizing client-centred tools such as the Canadian Occupational Performance Measure to explore occupational performance de cits in areas of self-care, productive roles, and leisure

Optimization of client-centred care is undertaken by observation of performance in a variety of environments such as home, school/institution of education, work, community, and clinical-based settings

Occupational therapy treatment—general overview

Functionally-focused treatments to enable occupational engagement—this involves working with the individual to address barriers to such engagement

Treatments aimed at ameliorating the identi ed barriers through functional restoration or adaptive approaches targeting the individual and the environments in which they engage

Group- or individually based and across the developmental life span

Occupational therapy treatment—speci c strategies

Provision of pain education, based on current neuroscience evidence, suitable for the person's level of health literacy and their cultural beliefs

Collaborative functional goal setting and goal action planning

Environmental modi cation (home, community, work, or school) to support function

Consideration of assistive devices to support or enable an individual's level of function. This may also include prescription of equipment, construction of splints, and provision of support garments

Sensory integration, processing, and modulation techniques to assist individuals in self-organizing their sensory system in order to optimize occupational performance. This may also include the use of graded motor imagery, sensory desensitization techniques, graded activity approaches, and development of improved interoceptive awareness

Creation of daily routines to support the development of habits and roles that support independence

Incorporation of psychological strategies that support functional independence such as CBT, ACT, cognitive restructuring, distraction, relaxation, and mindfulness techniques

Use of biofeedback techniques to support improved awareness of activity performance. This may include use of mirrors, EMG biofeedback machines, HR monitors, activity monitors, and diaries

Chronic disease self-management strategies such as:

- Joint protection
- Back care techniques and ergonomic principles
- Sleep management
- Energy conservation/fatigue management
- Pacing education: strategies are developed, considering the individual's functional needs, capacities, and opportunities for support and assistance. Such techniques are then embedded in the individual's habits and routines to maximize compliance over time
- Flare-up management

Support for return to work and productive roles on the background of a persisting pain condition

Support for return to school and study from preparatory through to university-level education

Support for resuming independent community engagement, including driving public transport use, shopping, and nancial management

Enabling the individual to reconnect with others in their social network and intimate relationships

Enabling the individual to locate appropriate, non-medical/health-based services within their local community that support self-management of their condition. Examples include local t'ai chi groups, linking into leisure interests, and nding social networks

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31.3 Graded exercise therapy and therapeutic exercise

De nition

Therapeutic exercise

Comprises of a series of speci c body movements, postures, or physical activities intended to provide the patient with the ability to:

- Improve, restore, or enhance physical function
- Prevent impairments
- Prevent or reduce health-related risk factors such as diabetes
- Optimize overall health and well-being and tness

Graded exercise therapy (GET)

GET is a method of delivering therapeutic exercise

GET is a therapeutic exercise that starts very gradually and increases slowly over a period of time

This approach is used widely in the treatment of long-term conditions such as bromyalgia syndrome, chronic fatigue syndrome (CFS), and myalgic encephalomyelitis (ME), as well as many acute injuries

Grade exercise programmes should be properly supervised by the physiotherapist and progressed according to the levels of discomfort and disability

There are four main types of exercise:

Passiveexercise —the joints and muscles are moved without e ort from the patient, usually from an external force such as a machine or the therapist

Isometric(static)exercise —the joint does not move when the muscle is tensed, with very little changes in the length of the muscle

Isotonic(dynamic)exercise —the joint is moved by the patient against constant resistance either from the physiotherapist or an apparatus. It is progressive

Isokineticexercise —this is a type of strength training which uses specialized equipment, or dynamometers, in order to maintain and control muscle contraction. The speed of the motion is always kept the same, even as the resistance alters

Pacing

Pacing is a graded approach which aims to avoid the 'boom-bust' cycle of over-exercising when the pain is at a reasonable level. This inadvertently leads to a are-up in pain levels and a period of relapse until the pain settles back down to a more manageable level and the cycle begins all over again

NICE (2007) de nes pacing as 'energy management, with the aim of maximising cognitive and physical activity, while avoiding setbacks/relapses due to overexertion.' It says, 'The keys to pacing are knowing when to stop and rest by listening to and understanding one's own body, taking a exible approach and staying within one's limits; di erent people use di erent techniques to do this'

Pacing is used widely in pain management in order to facilitate a patient's ability to participate in an exercise programme, be it home- or group-based, without causing an increase in their pain levels

Adaptive pacing therapy involves both the patient and the health care professional initially working together in order to facilitate the patient in their activity and functional levels, with the intention to achieve self-management

The Pain Toolkit describes pacing as one of the key tools to self-management of a chronic pain condition and activities must be balanced with periods of rest

E ectiveness

Level of evidence: 1A

Evidence supports the use of exercise for many long-term conditions, including bromyalgia and lower back pain

Currently there are insu cient data to be able to strongly state whether a speci c type of exercise is more superior in the treatment of chronic pain

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31.4 Functional restoration programme

De nition

FRP is a combined physical and psychological treatment programme recommended for patients with persistent back pain

It is o ered either in groups or as one-to-one

NICE guidelines state that a 'key focus is helping people with persistent non-speci c low back pain to self-manage their condition'

Patients who complete the programme should become experts at self-managing their condition, not require ongoing physical treatment, and be more likely to maintain a better health-related QoL

Inclusion criteria

Adults (i.e. over 18-year olds) with persistent back pain of >12 weeks' duration

Early management has not been e ective, i.e. the patient has failed to respond to routine primary care managements such as GP advice, medications, and physiotherapy-based exercise regime

The patient appears motivated in helping themselves to get better and has identi ed some clear goals

The patient has modi able psychosocial factors impacting on their ability to recover such as fear-avoidant pain behaviours, catastrophizing, etc.

Work status—the patient is:

- Either at work, paid or voluntary, but struggling to remain
- O work, but jobs remain open
- Not employed, but actively seeking to improve function and QoL

Exclusion criteria

Biomedical factors, including:

- Serious spinal pathology such as tumours, infection, and cauda equina signs
- Signi cant motor radiculopathy and signs of nerve root compromise requiring surgery
- Rheumatological conditions
- Other medical problems which would prevent involvement in physical exercise programme such as unstable heart conditions, signi cant respiratory problems, and poorly managed diabetes

Communication barriers which would prevent the ability to follow the cognitive component of a programme

Widespread multi-joint pain or bromyalgia-type conditions

Examples of other episodes of care:

No other open episodes of care for the same condition

No previous attendance to Pain Management/Self-Management Programmes

Treatment format and frequency

Patients are asked to complete a biopsychosocial assessment prior to being accepted into the FRP

Groups usually consist of up to 12 patients; classroom and gym-based

Patients generally attend for around eight sessions. The frequency of the programmes can di er, but commonly groups run twice a week over a 4-week period, with the total programme time being around 12 hours

Patients attending individual sessions with the physiotherapist typically attend ve sessions

Group intervention

The group intervention is generally provided by an interdisciplinary team which includes a doctor, a pain counsellor, and a physiotherapist

Group format

The session includes education regarding the biology of pain, participation in physical exercise sessions in small groups, graded activity, management of are-ups, and goal setting

Patients are taught relaxation skills and introduced to the concepts of visualization or mental imagery and mindfulness to help with their rehabilitation

Visualization—our mind plays an important role in the creation of our experience and therefore, it may be possible to 'programme' our mind and body to act in a certain way to gain positive results such as pain relief

Mindfulness—is a way of paying attention to, and seeing clearly, what is happening in our lives. It will not eliminate life's pressures, but it can help us respond to them in a calmer manner that bene ts our general health and well-being

Outcome measures

The Oswestry Low Back Pain Disability Questionnaire (Oswestry Disability Index (ODI))

Is an important tool that researchers and disability evaluators use to measure a patient's permanent functional disability

The test is considered the 'gold standard' of low back functional outcome tools

The Pain Self-E cacy Questionnaire (PSEQ)

A 10-item questionnaire, developed to assess the con dence people with ongoing pain have in performing activities while in pain

For PSEQ scores of around 40 and above, there has been an increased association between patients returning to work and maintenance of functional gains

Medication reduction

Is also a key goal to achieve in those patients who attend FRP

Typical data demonstrate that approximately three-quarters of patients manage to reduce their analgesic medication following attendance to the programme

E ectiveness

Level of evidence: 1A

There is moderate-quality evidence that multidisciplinary interventions result in greater improvements in pain and daily function

There is also moderate evidence to support return to work, compared to treatments aimed at physical factors alone

Further reading

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31.5 Hydrotherapy

De nition

Hydrotherapy is the use of water for treatment of many di erent conditions such as OA, RA, persistent lower back pain, and bromyalgia syndrome. It is also used to treat patients post-surgery and post-trauma injuries such as fractures

Aquatic exercise is de ned by the Chartered Society of Physiotherapy (CSP) as a 'therapy programme designed by a quali ed physiotherapist using the properties of water to improve function ideally in a suitably heated pool'

Balneotherapy is use of hot water treatment to help reduce pain, with the addition of various other techniques such as various forms of salt or sulphur, mud packs, jet streams, etc.

Temperature of the pool

The maximum temperature of the pool should not exceed 35°C, with a maximum of 60% humidity

The external pool temperature should be between 25°C and 28°C

Therapists should not spend >3 hours per day in the pool itself

Therapeutic e ects of hydrotherapy

The physiotherapist uses speci c properties of water in order to develop a therapeutic graded exercise programme

The thermal e ects of water are considered to help relieve pain, facilitate movement, and enhance relaxation

The simple act of body part submergence increases energy expenditure

Exercise intensity can be increased with the use of equipment such as paddles and oats

Speci c properties of water include:

- *Buoyancy*—with or without a buoyancy aid; can be used to assist or resist movements
- *Resistance*—water viscosity also provides resistance against movements. Resistance can be increased or decreased by changing the speed or directional use

Flow—the use of water jets to alter ow can modify the amount of resistance provided during treatment

Turbulence—the more turbulence created using methods such as water jets or speed alteration, the greater the energy expenditure

Physiotherapy-prescribed exercise programmes

Following assessment, the physiotherapist will instruct the patient on an appropriate treatment programme that the patient can perform independently

Exercises should then be reviewed at regular intervals in order to modify the exercise programme, depending on the patient's condition and rate of progress required

Frequently, a patient's hydrotherapy management will be integrated into an appropriate land-based exercise regime

Contraindications/precautions to hydrotherapy

All patients should have an initial screening and a land-based physiotherapy assessment in order to determine their suitability for hydrotherapy before entering the water; this is to ensure patient suitability and safety maintenance

The following areas should be assessed prior to therapy:

CVS (e.g. BP, cardiac problems)

Respiratory system (e.g. asthma, chest infections)

CNS (e.g. epilepsy, tonal changes)

GI tract (e.g. incontinence, infection)

Genitourinary tract (incontinence, infection, pregnancy)

Infectious conditions (e.g. methicillin-resistant *Staphylococcusaureus* (MRSA), herpes)

Skin conditions (e.g. surgical wounds, rashes, chemical sensitivity)

Eye and ear conditions (e.g. tubal implants, visual or hearing impairments)

Other conditions (e.g. fear of water, diabetes, mode of pool entry, psychiatric problems)

E ectiveness

Level of evidence: 1A

There is moderate-quality evidence that aquatic exercise may have an e ect on patient-related outcomes in knee and hip arthritis

There is low- to moderate-quality evidence that aquatic exercise is bene cial for improving wellness, symptoms, and tness in adults with bromyalgia

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31.6 Graded motor imagery and mirror box therapy

De nitions

Imagery refers to the creation of an experience in the mind (auditory, visual, tactile, olfactory, and gustatory). It is a cognitive process used by humans

Motorimagery (MI) is the mental representation of movement without any body movement.
It is a highly complex cognitive process, which is self-generated using sensory and perceptual processes, facilitating the activation of speci c motor actions to improve motor function
Evidence suggests that MI has positive e ects on motor performance in athletes, people who are healthy, and people with neurological conditions

Graded motor imagery (GMI)

GMI is a sequential approach to MI, an individually tailored treatment process which has been used successfully for persistent and complex pain states
It aims to give exibility and creativity back to the brain via graded exposure and is commonly used in the treatment of CRPS
It is composed of three separate phases:

- The rst phase consists of patients learning to recognize images of their left or right hands or feet which are shown to them in various positions
- The second phase consists of patients practising these positions via MI of smooth and pain-free movements
- In the third and nal phase, they perform movements of both limbs using a mirror box to hide the a ected limb

Mirror box therapy

Mirror therapy means looking into a mirror to see the re ection of the limb or body part in front of it
Brain activation during mirror therapy is less than during actual movement, but slightly more compared with imagining the same movement
The patient places their a ected limb inside the mirror box and works through a series of movements
Looking at the mirror image of the una ected limb gives the illusion of seeing the hidden a ected limb
In the initial phases of rehabilitation when the limb is at its most sensitive—the a ected limb will be kept still inside the mirror box, while the una ected limb outside the box will be performing tasks such as rotation, nger opposition, making a st, wrist movements, etc.
As treatment progresses, resistance can then be added, e.g. making a st but adding in a squeeze in repetitions
The a ected limb will gradually start to join in the movements within the patient's pain limitations
As the a ected limb becomes less sensitive, the roles then reverse and the una ected limb starts to copy the movements of the a ected limb while it remains inside the box

Frequency of intervention

For a general guide, studies have used a period of 2 weeks for each of the phases of GMI and have advised around 10 minutes for each waking hour
In essence, there is no set frequency for mirror box therapy and treatment is focused very much on the individual's needs

E ectiveness

Level of evidence: 1A
Currently the quality of available evidence is variable
There is a recognized need for further research

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31.7 Acupuncture and electro-acupuncture

Definition

- Acupuncture is the process of having fine needles inserted into certain sites in the body for therapeutic purposes. These sites are known as acupuncture points
- Derived from ancient Chinese medicine and forms part of traditional Chinese medicine (TCM)
- Practitioners of TCM believe that stimulating certain acupuncture points can help restore the balance between Yin and Yang that can become disturbed in illness or pain
- More often, scientific *evidence-based western medical acupuncture research* is combined with the principles of TCM as a means to help reduce pain and enhance other treatments such as exercise and functional-based activities
- The Bladder Meridian which is commonly used for lower back pain (see Figure 31.7.1)

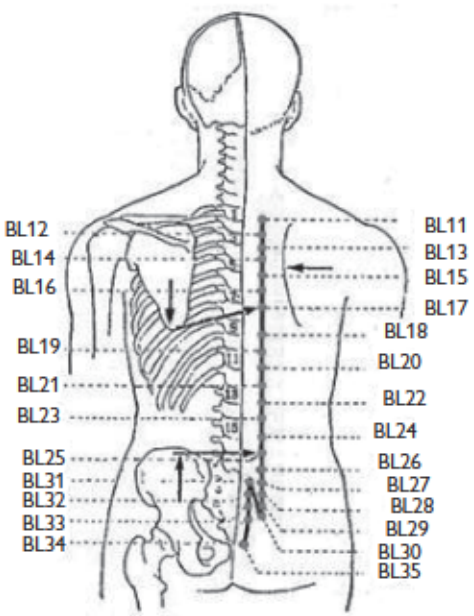


Figure 31.7.1 Bladder Meridian (commonly used for lower back pain)
Copyright © Natural Health Zone, http://www.natural-health-zone.com/bladder-meridian.html

Acupuncture practitioners

Acupuncture practitioners are most often physiotherapists, GPs, and nurses who have attended appropriate accredited training courses

Recognized professional bodies for trained acupuncturists include:

- British Acupuncture Council (BAcC)
- British Medical Acupuncture Society (BMAS)
- Acupuncture Association of Chartered Physiotherapists (AACP)

Indications

MSK conditions

Spinal pain, joint pains

Widespread body pains such as bromyalgia syndrome

Migraines and tension-type headaches

Acupuncture should be used alongside other treatments such as exercise therapy, manual therapy, and education, as well as relaxation techniques, in order to enhance outcomes and facilitate self-management.

Theoretical mechanism

Acupuncture stimulates the body to produce chemicals, which act to help relieve pain, reduce stress, and promote restful sleep, and to help produce a positive feeling of well-being. These chemicals include:

- Endorphins: endogenous opioid neuropeptides found to be natural pain relievers and also to promote feelings of pleasure and euphoria
- Oxytocin: hormone which has antidepressant-like e ects
- Melatonin: hormone that regulates sleep and wakefulness
- Serotonin: monoamine NT which is thought to be a contributor to feelings of well-being and happiness

Correlation has also been found between certain acupuncture points and myofascial trigger points

Contraindications

Pregnancy—in the rst and last 3 months and patients trying to conceive

Pacemaker or any other electrical implant (no electro-acupuncture)

Any damage to heart valves

Risk of active infection or patients with a de cient or weak immune system, known skin infection, or poor skin condition in the area of treatment

Known metal allergy

Needle phobia

Oedematous limb(s)

Precautions

Fit, seizure, faint, or epilepsy

Diabetes, low BP

On anticoagulation or antiplatelet therapy, or a bleeding disorder, e.g. haemophilia

Generally feeling unwell or with cold/ u symptoms

Patients who are going to drive or operate machinery after treatment
Malignancy

Number of sessions

Most patients will receive between four and six sessions at weekly intervals
Sometimes patients are o ered top-up sessions
If no noticeable bene ts after the rst 2–3 acupuncture sessions, then treatment should be stopped

Safety and side e ects

Mild and short-lived S/Es—fatigue, light-headedness/nausea/dizziness, bruising, localized bleeding, redness around the needle site, and mottling of the skin
Rare S/Es—infection, allergic response to the metal
Extremely rare—pneumothorax

Electro-acupuncture

Insertion of needles that are coupled to electrodes attached to an electro-acupuncture machine
These units deliver variable amplitudes and frequencies of electrical impulses
Low-frequency electro-acupuncture contributes to the mechanism of delayed pain reduction by stimulating the production of endorphins
High-frequency electro-acupuncture works via the serotonin route and is more quick-acting
Electro-acupuncture may be more useful in persistent pain conditions

Further reading

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31.8 Laser therapy

De nition

LASER is an acronym for Light Ampli cation by Stimulated Emission of Radiation. Laser is therefore a form of light ampli er which provides enhancement of particular properties of light energy
Therapy lasers can be categorized into a particular category of laser light known as 3A or 3B and are referred to as low-level laser therapy (LLLT)
LLLT does not cause a detectable rise in temperature in the targeted tissues, nor does it cause any macroscopically visible changes in tissue structure. It is therefore considered to be a non-thermal modality
LLLT is used as a therapeutic treatment to help reduce pain and disability associated with MSK and joint diseases, including lower back pain

Parameters

Most LLLT devices generate light in the red visible and near infra-red bands of the electromagnetic spectrum, with typical wavelengths of 600–1000 nm

The mean power of the therapeutic machines is typically low (1–100 mW), but the peak power could be much higher

Treatment devices

The treatment device may be a single emitter or a cluster of several emitters

The output may be pulsed or continuous

Lower pulsing rates are more e ective for acute conditions, while higher pulsing rates work better for more chronic conditions

Mode of action

When LLLT is applied to the body tissues, it delivers energy at a level appropriate enough to disturb local electron orbits, which results in the production of heat

This subtle change in uences the cell membrane and can initiate a chemical change, disrupt chemical bonds, and produce free radicals

LLLT is thought to a ect broblast function and accelerate connective tissue repair

There are also some reports that LLLT has anti-in ammatory e ects as a consequence of its action in decreasing PG synthesis

LLLT is mainly absorbed by super cial tissues, but it could possibly have a deeper e ect. However, the exact mechanism for this action remains inconclusive; theories include chemical mediators or second messenger systems

Clinical application

Laser therapy is generally used for the following conditions:

- Wound healing
- In ammatory arthropathies
- Soft tissue injuries
- Pain conditions such as myofascial trigger point pain and bromyalgia syndrome

Precautions/contraindications for laser therapy

Precautions should be noted when treating the following:

- Pregnancy (anywhere on the body)
- Active implants, including pacemakers
- Metal implants
- Epilepsy
- Local circulatory insu ciency/devitalized tissue

Contraindications include:

- Over the eyes and testis
- Pregnancy (around the fetus)
- Malignancy
- Active epiphysis
- Active bleeding tissue

E ectiveness

Level of evidence: 1A

Currently there are insu cient data to either support or refute the use of LLLT in the treatment of chronic pain conditions

There is a recognized need for further research

Further reading

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SECTION 9

EPIDEMIOLOGY AND STATISTICS

CHAPTER 32

Epidemiology and Statistics

Sabina Bachtold, David Pang, and Ali a Tameem

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32.1 Epidemiology of chronic pain

Introduction

Chronic pain is one of the most signi cant causes of long-term su ering and morbidity

Despite its high prevalence, it remains under-recognized and poorly resourced, compared with other chronic medical conditions

This is despite chronic pain being one of the most important causes of disability and work-related days o

Precision in measurement of the prevalence and incidence of pain is hampered by many factors:

- Pain is a subjective measure, and self-reported measures of pain are used to measure both intensity and occurrence
- A level of pain that is signi cant to one individual cannot be reliably replicated on another

Accurate measurement of prevalence and incidence of chronic pain and their causes is essential to direct healthcare policies and initiatives to improve the outcome of any interventions directed at relieving the morbidity of chronic pain

In 2006, a large survey of 46 349 Europeans from multiple countries revealed that pain over 6 months was prevalent in 19% of all responders

A recent meta-analysis estimated the prevalence of chronic pain in the UK as 43%

The prevalence rises with age, and 10.4–14.3% of the population had pain that was moderate to severe

It is likely that these numbers are an underestimation, yet most of chronic pain is managed in primary care or without help from health care professionals

Multiple factors are associated with chronic pain, and many of our current therapies are directed at these factors, as well as at the pain itself

Clinical factors

Chronic pain is now recognized as a disease in its own right, and not merely a symptom of another underlying problem

One of the most important factors associated with chronicity is the severity and existence of multiple painful areas

The association of chronic pain with other long-term diseases is well established and patients with severe chronic pain have a doubling of mortality from cardiorespiratory illness over a 10-year period

Psychological factors

The relationship between mental well-being and chronic pain is likely to be bidirectional

Mental health conditions and patient beliefs play an important part

Poor prognostic indicators include anxiety, depression, catastrophizing, and avoidance beliefs

Interventions directed at using active, rather than passive, coping strategies to target beliefs about chronic pain can be more e ective

Large public health interventions with the aim of changing attitudes and beliefs about chronic pain have shown mixed results

Social factors

A higher prevalence of chronic pain is seen in:

- Females
- Increasing age
- Low socioeconomic status
- Unemployment
- History of abuse

Ageing of the population will have implications on pain management resources, as older age is associated with more chronic pain

Many of the above factors cannot be altered, but recognizing their association with pain will assist in the provision of pain services

Genetics

An increasing body of research has shown that genetic factors can play a signi cant role in chronic pain

Children of parents with chronic pain show an association, and genetics play a part in determining pain thresholds

Speci c pain conditions

Low back pain

A point prevalence of 11.9% and a lifetime prevalence of 39.9% were measured in a large global study in 2012

This increases with age, with implications for health care provision for an ageing population

Most episodes of low back pain are self-limiting, but relapses are common

There have been associations with smoking, job dissatisfaction, psychological comorbidity, low physical conditioning, and coexisting medical conditions

Neuropathic pain

An estimate of the prevalence in the general population is 1.5%, but neuropathic pain varies with the underlying condition:

- Most common are neuropathic low back/leg pain and diabetic neuropathy
- Patients with neuropathic pain consume more health care resources and have a lower QoL, compared with matched controls

Chronic widespread pain and bromyalgia

This is the second most common rheumatic disorder after OA

There is a female:male ratio of 2:1, and it is seen in both paediatric and adult populations

No signi cant di erence exists between di erent cultures, ethnic groups, or countries

Genetic factors may play a role as rst-degree relatives have a higher risk of developing bromyalgia (odds ratio (OR) 8.5)

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32.2 Evidence-based medicine

Introduction

De nition as '*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients*'

Integrates the clinician's expertise, the patient's values, and best research available to improve patient care

Levels of evidence

Highest level of evidence must be sought unless the evidence is minimal and/or of low quality

GRADE methodology

The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) working group has explained the quality of evidence which is used to develop good-quality EBM

SIGN methodology

The Scottish Intercollegiate Guidelines Network (SIGN) follows the principles of GRADE methodology to assess the overall quality of evidence

The working group were responsible for creating a grading system for recommendations, linked to the strength of evidence available. International and national guidelines for best practice use the SIGN methodology

Quality of evidence

Based on robustness of the techniques used and depends on multiple factors:

- Design of the study—minimal bias and maximum credit to the question posed
- Quality of the study—poor randomization, non-blinding, and inappropriate statistics used would lead to poor-quality studies
- Consistency—similarity of estimate of e ect
- Directness—properly matched patients to the interventions

Follow a **typical** 'hierarchy of evidence' (see Table 32.2.1)

Table 32.2.1 Hierarchy of evidence

Levels	Evidence
1	At least one published systematic review of many well-designed randomized controlled trials (RCTs)
2	At least one published well-designed RCT of good size and appropriate setting clinically
3	Non-randomized, published, well-designed trials, cohort study, or case-controlled studies
4	Well-designed, non-experimental studies from multiple centres or research groups
5	Descriptive studies, expert opinions, consensus committee reports, anecdotal evidence from case reports

Strength of recommendation essentially informs us whether an intervention should be applied or not. It depends on the quality of evidence described above, trade-o s (balance between risks and bene ts), speci c patient groups belonging to speci c situations, and the amount of baseline risk in the speci c population

Limitations/criticisms of EBM

Publication bias can be responsible for unpublished negative trials, hence not a true re ection of EBM

Research progress can be limited due to ethical and cost implications

RCTs or meta-analyses cannot always answer all hypothetical questions

A well-designed RCT can be expensive and sometimes una ordable

Pharmaceutical companies provide a lot of nancial support, which can further introduce bias and con ict of interest

Health economics has a role in the current climate and the best evidence for treatment may not necessarily be the 'best value for money'. This has implications for appropriate management of patients as per EBM

Although guidelines and recommendations provide safe evidence-based pathways, they cannot always be applied to all clinical scenarios, especially in unique settings, and clinical acumen is still required

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32.3 Statistics

Introduction

It is a mathematical science which allows the data (numerical information) to be presented, analysed, and interpreted to draw conclusions

- Parameter—a characteristic of a population which can be measured
- Variable—a characteristic of a sample which can be measured, varies between individuals, and can be quantitative or qualitative
- Sample statistic—a mathematical calculation of the data variables of a given sample

Types of data

Numerical (quantitative) data

- Presented as tables, cumulative frequency curves, histograms, and plots (dot plots, x–y scatterplots)
- *Discrete data* have finite values (number of children)
- *Continuous data* can take any numerical value, including fractional values (weight, height)
- *Ratio data* series have zero as the baseline value (length, Kelvin temperature scale)
- *Interval data* series include zero as a point on a larger scale (Celsius temperature scales)

Categorical (qualitative) data

- Presented as tables (contingency table) or graphically as pie charts and bar charts
- *Nominal data* can only be named (ABO blood groups or different types of fruit)
- *Ordinal data* have an implicit order of magnitude (pain—nil/mild/moderate/severe or American Society of Anesthesiologists (ASA) score)

Describing data

Measures of central tendency

(See Fig. 32.3.1.)

- *Mean (average)*:
  - The sum of data values divided by the total number of data points
  - Used to analyse interval data, especially when normally distributed
  - Uses all data but is readily influenced by outliers

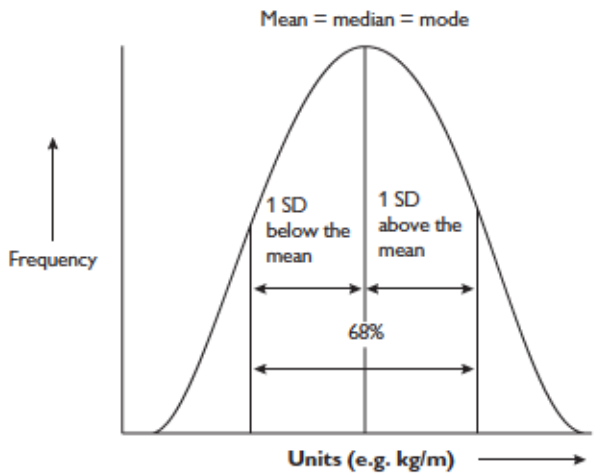


Figure 32.3.1 An example of Gaussian/normal distribution. One standard deviation (SD) refers to one SD above and below the mean; 2 SD = 96% of the population; 3 SD = 99.6%

Median:

The middle value of a data series when arranged in a ranked order, with 50% of data points above and 50% below

It is not readily in uenced by outliers but does not make use of all individual data values

It is a helpful measure of central tendency for ordinal and interval data

When the interval data set is not normally distributed, the median is preferred over the mean

Mode:

The most frequently occurring value in a sample

It is not used much in statistical testing

It measures a frequently occurring value in a sample set, used mainly for categorical data

Measures of spread

The Gaussian curve is the most useful bell-shaped graphical representation of interval data in statistics. If symmetrical, mean = median = mode, and the data is normally distributed

Parametric, normally distributed data—mean and standard deviation are suitable

Non-parametric data—median and interquartile range are appropriate

Parametric skewed data—treat as non-parametric data or attempt to mathematically convert to normally distributed data

When unsure whether the data are parametric, especially with small sample sizes, apply non-parametric analysis

Standard deviation (SD):

A measure of the spread of data around a central point

$$SD = \sqrt{\frac{\Sigma(mean - x)^2}{n \text{ or } n-1}}$$

Where: mean x = the di erence from the sample mean for each value; n = number of observations or sample size; Σ = sum of. n 1 is used if the number of observations is 30; n is used if >30 observations. 1 SD = 68% of the population; 2 SD = 95.7%; 3 SD = 99.7%

Variance = $(SD)^2$

A measure of the spread of data around a central point

Con dence intervals (CI):

The range of values that will contain the true population mean with a stated percentage con dence

95% CI is the sample mean ± 1.96 SD (or SEM) and is the most frequently quoted

Standard error of the mean (SEM):

$SEM = SD/\sqrt{(n)}$

Measures how precisely the sample mean is estimated (how far from the population mean). It is not a measure of spread of the data

Percentile:

The data are arranged in a ranked order and then divided into 100 points called percentiles

Each quarter (25%) is a quartile and the interval data are well represented by a box and whisker plot

Quartile:

One of the three values that divide a given range of data into four equal parts—lower, middle, and upper quartile at 25th, 50th, and 75th percentile, respectively

Interquartile range (IQR):

The data are ranked (i.e. put in order from lowest to highest) and divided into quarters

The IQR is the range between the lowest and the highest quarters (i.e. encompassing the middle half of the data)

If a dividing point is between two numbers, then an average is taken

Range:

The simplest form of a measure between the lowest and highest value, minimal statistical value

Statistical tests

(See Table 32.3.1.)

Parametric tests

Used for samples which contain data with a normal distribution

Non-parametric tests

Do not rely on assumptions about the shape or parameters of the underlying population distribution

The null hypothesis (H_0)

When performing a study, the first step is to pose a question, which is formulated as a hypothesis that must be proved or disproved

This question represents the null hypothesis and it states that there is no difference between the sample groups

Table 32.3.1 Statistical tests

Sample group(s)	Parametric tests	Non-parametric tests	Categorical data tests
One group	One-sample t-test	Wilcoxon signed rank test	
Two groups	Unpaired normal distribution data: Student's unpaired two-sample t-test Paired normal distribution data: Student's paired two-sample t-test	Mann–Whitney U test (unpaired t-test) Wilcoxon signed rank test (paired t-test)	Unpaired data: Fischer exact test Paired data: McNemar's test
Three or more groups	ANOVA (analysis of variance)	Kruskal–Wallis Friedman	Pearson's chi-squared test (χ^2)

Power

The ability of a statistical test to reveal a di erence of a certain magnitude
Power is (1 β) × 100% and acceptable power is 80–90% (β = probability of type II error)

Type I error

There is no di erence between the sample groups, but a statistical di erence is found, as P <0.05
The null hypothesis is incorrectly rejected, leading to a false positive result
The probability of making a type I error is called Alpha (α)

Type II error

There is a di erence between the sample groups, but a statistical di erence is found, as P >0.05
The null hypothesis is incorrectly accepted, leading to a false negative result
It is usually because of a small sample size
The probability of making a type II error is called Beta (β)

P value

The likelihood of the observed value being a result of chance alone
Conventionally, a P (probability) value of <0.05 represents statistical signi cance, P <0.01 highly signi cant, and P >0.5 not signi cant
It is important to distinguish statistical signi cance from clinical signi cance

Risk

It is the probability or likelihood that an event may occur
If RR >1, treatment group is better
Absolute risk reduction (ARR) suggests that the incidence of e ect is mainly due to the treatment
Relative risk reduction (RRR) re ects the amount of risk that is removed by the treatment group

Relative risk (RR) = incidence in treatment group/incidence in control group
Absolute risk reduction (ARR) = incidence in treatment group incidence in control group
Relative risk reduction (RRR) = absolute risk reduction/incidence in control group
Odds ratio (OR) = odds of outcome in treatment group/odds of outcome in control group

Number needed to treat (NNT)

Number of patients who need to be treated to achieve an outcome in one patient
NNT of 1 is the perfect outcome, but very di cult to achieve clinically
The closer the treatment group to NNT of 1, the better the treatment

Number needed to harm (NNH)

Number of patients who need to be treated (or exposed to a risk factor) in order for one person to have a particular adverse e ect
An NNH of 6 for minor adverse e ects for amitriptyline means that for six patients treated with amitriptyline, one experiences minor adverse e ects (e.g. drowsiness, dizziness, dry mouth, constipation)
The lower the NNH, the more the risk of harm
An NNH of 1 would mean that every patient treated is harmed

Table 32.3.2 Methods of data analysis

Test outcome	Positive	Negative
Positive (P <0.05)	True positive (TP)	False positive (FP) (type I error/α)
Negative (P >0.05)	False negative (FN) (type II error/β)	True negative (TN)

Outcome prediction

(See Table 32.3.2.)

Sensitivity

The ability of a test to correctly identify a positive outcome when one exists

$$\text{Sensitivity (\%)} = TP/(TP + FN)$$

Where: TP = true positive; FN = false negative

Speci city

The ability of a test to correctly identify a negative outcome where one exists

$$\text{Speci city (\%)} = TN/(TN + FP)$$

Where: TN = true negative; FP = false positive

Positive predictive value (PPV)

The certainty with which a positive test result correctly predicts a positive value

$$\text{PPV (\%)} = TP/(TP + FP)$$

Negative predictive value (NPV)

The certainty with which a negative test result correctly predicts a negative value

$$\text{NPV (\%)} = TN/(TN + FN)$$

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32.4 Clinical trials

Clinical trial design

De ne the problem that needs to be addressed by carefully observing clinical work

Formulate a null hypothesis by choosing the correct research question

Perform a literature search

Obtain Ethics approval

Types of Clinical Studies (see Table 32.4.1)

Retrospective studies are helpful with rare disorders and are less expensive than prospective studies as they can utilize existing resources

However, obtaining accurate and complete information without bias is di cult as there can be many confounding variables

Trial planning and design (statistician/methodology expert involved)

Write a protocol detailing how the trial will be conducted

Ideally it should be a double-blinded, randomized, case-controlled trial

Estimate the number of patients required to perform the study and avoid a type II error (power calculation). An adequately powered study will ideally detect an e ect in 80% of the times if it exists

Risk assessment

Sponsorship

Ethics approval by completing the online research application form on the Integrated Research Application System (IRAS)

Analysis of data to assess statistical and clinical signi cance. Traditionally, $P < 0.05$ has been used to determine statistical signi cance, as there would be a <5% chance that the null hypothesis has been wrongly rejected

Over time, CIs are calculated to summarize the statistical signi cance

Clinical signi cance is based on standards of care and expert opinions

Reporting and dissemination of results—guidance provided by Consolidated Standards of Reporting Trials (CONSORT)

Publication bias can occur when negative trials or statistically insigni cant trials are not published. An inverted, symmetrical funnel plot of individual studies would suggest that all studies have been included, minimizing selection or publication bias

Table 32.4.1 Types of clinical studies

Retrospective	Prospective
Cross-sectional studies or surveys (a random group or a well-de ned population is studied) Case-control studies (a speci c condition is compared to the controls)	Observational cohort studies (two or more groups are studied over a long period) Randomized interventional control studies (evaluate the interventional arm of the study and reduce bias) Non-randomized or cohort interventional controlled trials (evaluate interventions but can have an element of bias)

Table 32.4.2 Phases of clinical trials: preceded by *in vitro* and animal studies

Phase	Participants and purpose	Number of subjects
0	Optional exploratory trials (human micro-dosing) Does the drug behave in humans as was expected from preclinical studies?	10–15
1	Healthy volunteers/people with the disease Safety and dosage	20–50
2	People with the disease E cacy and side e ects	Several hundreds
3	People with the disease E cacy and monitoring adverse reactions	300–3000
4	People with the disease Safety and e cacy (post-marketing surveillance)	Several thousands

Phases of clinical trials (see Table 32.4.2)

Types of trials

Case-control studies

Observational study comparing patients; can be done rapidly for rare conditions

Case reports or series

Reports of a patient or group of patients based on similar events

They provide clinical management tools for rare conditions, but lack group comparisons and are not generalized to all patients

Cohort (longitudinal) studies

Can be retrospective or prospective where people belong to the same group, but have an intervention and a control arm. It can be open to bias and the work is time-consuming since a large sample size is needed

Randomized controlled trial

Ideally, it should be:

Blinded:

In double-blinded trials, neither the observer nor the subject are aware of the treatment and thus may not bias the result

Randomized:

This avoids any bias in the allocation of treatments to patients. It guarantees that the probabilities obtained from statistical analysis will be valid

Randomization prevents the in uence of confounding factors (e.g. when the e ects of two processes are not separated)

Controlled:

This provides a comparison to assess the e ect of the test treatment

In many instances, the most appropriate control is a placebo, i.e. a tablet or medicine with no clinical e ect

Systematic review

It is an assessment, evaluation, and critical appraisal of various research studies and other relevant data available to address a speci c issue

It can be qualitative and o ers a summary to guide clinical decision-making

Meta-analysis

It is a quantitative measure where there is statistical integration of multiple similar research studies and can be graphically represented by Forest plots

It is useful when a good-quality, large, prospective, randomized study is unavailable. A meta-analysis can produce NNT and/or NNH

Further reading

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