Directions in

Psychiatry

CATEGORY 1
AMA PRA
Credit Hours

CME

VOLUME 36

Directions in Psychiatry

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hatherleigh

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62545 State Highway 10, Hobart, NY 13788

Learning Objectives Evaluation Form

Directions in Psychiatry, Vol. 36

Full Name: _____   Date: _____   Customer No:_____

**Please complete this evaluation form to help us assess how the CME lessons achieve
the intended learning objectives. To what extent were the learning objectives achieved?**

3 = good/high   2 = satisfactory/average   1 = poor/low

As a result of completing this course, participants will have:

CME Lesson 1: PTSD: Overview and DSM-5 Changes

_____ understood the history behind the conceptualization of PTSD and learned the factors that influenced the changes in its criteria over time.

_____ reviewed the risk factors, presentation, and pathophysiological changes associated with the condition.

CME Lesson 2: Substance Use Disorders: An Overview, and Changes in the DSM-5

_____ been able to distinguish some of the similarities and differences in the diagnostic criteria for substance use disorders in the DSM-IV-TR and the DSM-5.

_____ become enabled to recall the basic epidemiology and neurobiology of substance use disorders in adolescents and adults.

CME Lesson 3: Somatic Symptoms and Related Disorders: Overview, Updates, and Changes in the DSM-5

_____ described the new DSM-5 diagnostic criteria for Somatic Symptom and Related Disorders.

_____ compared changes from the DSM-IV-TR.

CME Lesson 4: The Meaning of Despair: Existential and Spiritual Dimensions of Depression and Its Treatment

_____ been enabled to assess for spiritual dimensions of a given patient's depression.

_____ understood the ethical considerations associated with spiritually integrated care.

CME Lesson 5: The Detrimental Impact of Maladaptive Personality on Public Mental Health: A Challenge for Psychiatric Practice

_____ reviewed the impact of maladaptive personality traits on mental health and functioning.

_____ appreciated the importance of early assessment of personality disorders which may abate the effects of common co-occurring psychiatric disorders.

CME Lesson 6: Treatment of U.S. Military Soldiers and Veterans: Basics of PTSD, Administrative Issues, and Cultural Competency

_____ reviewed the *Military Health System* (MHS) and *Veterans Health Administration* (VHA) systems of

_____ reviewed the updated definition of PTSD and be able to utilize evidence-based techniques outlined in this lesson in the treatment of PTSD.

CME Lesson 7: Meeting the Psychosocial Needs of Burn Survivors and Their Families

_____ gained a greater understanding of the psychological needs of patients with burn injuries at each stage of recovery.

_____ been able to match a nonpharmacological pain control intervention with a patient's coping style

CME Lesson 8: Synthetic Cathinone and Cannabinoid Designer Drugs

_____ reviewed recent evidence on the epidemiology, pharmacology, central nervous system effects, and other clinical findings and the regulation prevalence of synthetic drugs.

_____ been able to interpret the clinical findings and major symptoms and side effects of these drugs.

CME Lesson 9: Closing the Treatment Gap for Mental, Neurological and Substance Use Disorders by Strengthening Existing Health Care Platforms: Strategies for Delivery and Integration of Evidence-based Interventions

_____ reviewed a framework of integrated collaborative care using the World Health Organization's pyramid of self-care, primary care, and specialist care.

_____ reviewed a set of evidence-based interventions and strategies to implement these principles into practice.

CME Lesson 10: Recent Advances in Psychological Therapies for Eating Disorders

_____ reviewed the various forms of psychological therapies in the treatment of eating disorders such as *cognitive-behavioral therapy* (CBT) and family-based treatment, and assess their efficacy and outcomes.

_____ reviewed other forms of adjunctive therapies that are useful to include in a patients' treatment plan.

Learning Objectives Evaluation Form

Directions in Psychiatry, Vol. 36 (cont.)

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As a result of completing this course, participants will have:

CME Lesson 11: Psychiatrist as Expert Witness

_____ understood the circumstances calling for psychiatric expert witnesses.

_____ understood the difference between expert and fact witnesses.

CME Lesson 12: Acute Ischemic Stroke, Post-stroke Cognitive Deficits, and Depression

_____ defined *acute ischemic stroke* (AIS) and understood its causes.

_____ considered possible treatments and proactive interventions for AIS and cognitive defects.

CME Lesson 13: Intellectual Disability Disorder (IDD): From the DSM-IV to the DSM-5

_____ reviewed the new *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (DSM-5) diagnostic criteria for *intellectual disability disorder* (IDD).

_____ compared changes with the fourth edition of the same manual, DSM-IV-TR.

CME Lesson 14: Attention-Deficit Hyperactivity Disorder: Overview and DSM-5 Changes

_____ reviewed the history of and appreciated the prevalence of ADHD.

_____ distinguished the differences between the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) and DSM-5 diagnostic criteria for ADHD.

CME Lesson 15: Dissociative Disorders: Between Neurosis and Psychosis

_____ understood the various types of dissociative disorders, including recent changes made in the DSM-5.

_____ considered the history and current diagnostic criteria for dissociative disorders.

CME Lesson 16: The "Three Buckets" Model for Treating Posttraumatic Stress Disorder (PTSD): Medication, Therapy, and Everything Else

_____ been enabled to define PTSD and introduce a "three buckets" concept as an organizational framework for the variety of PTSD treatment options.

_____ considered the scientific basis for TMS as an emerging treatment for PTSD, and (4) identify additional resources to incorporate this technology into clinical practice.

CME Lesson 17: Chronic Pain, Cognitive Deficits, and Depression

_____ learned to define chronic pain and understand its causes.

_____ reviewed various cognitive deficits associated with chronic pain.

CME Lesson 18: Biomarkers in Alzheimer's Disease

_____ reviewed the current hypothesis for *Alzheimer's disease* (AD) pathogenesis, called the amyloid cascade.

_____ considered the need for and the availability and clinical utility of biomarkers of AD.

CME Lesson 19: Substance Use During Pregnancy

_____ reviewed the different types of substance abuse that occurs in pregnant women.

_____ considered the common co-occurring conditions and disorders that impact pregnant women with substance use disorders.

CME Lesson 20: Knowledge Transfer in the Field of Parental Mental Illness: Objectives, Effective Strategies, Indicators of Success, and Sustainability

_____ reviewed the need and complexities of establishing, implementing, and sustaining interventions to reduce the transference of mental illness from parents suffering from mental illness to their children.

_____ explored aspects of knowledge transfer, indicators of success, and continuance.

CME Information Page

The objective of this continuing medical education program is to present participants with an expanded clinical skill set and raised awareness of clinically relevant issues in their profession. They will review key diagnostic criteria, cutting-edge treatment strategies, and practice points they can implement in the challenges of daily practice while providing evidence-based care to patients and clients suffering psychiatric and comorbid medical disorders. The expected outcomes include an increase in knowledge, competence, professionalism, and performance.

Target Audience: The primary target audience for this program includes, but is not limited to: psychiatrists, primary care physicians, psychiatric nurses, pharmacists, clinical psychologists, and social workers. Clinicians who have caseloads composed significantly of individuals with psychiatric disorders, and comorbid medical illnesses will find this course particularly useful.

Duration of CME Status: *Directions in Psychiatry* **begins May 28, 2015,** and the *preliminary* **expiration date is December 31, 2021.** At that point, the Hatherleigh Medical Director and the editorial staff will review the CME material to determine whether the program continues to be consistent with current accreditation guidelines and standards **Overall Objective:** of care. A determination will be made as to whether the program can be used to earn full CME credit after that date.

Conflict of Interest Disclosure Policy

Faculty members were selected for their expertise and, most often, on the strength of their presentations from previously published papers or symposia. Hatherleigh Medical Education staff, contributing program faculty, and advisory board members, must disclose their relationships (also on behalf of their immediate family members), if they exist, with commercial and/or pharmaceutical companies prior to Hatherleigh Medical Education's distribution and publication of their contributions to Hatherleigh Medical Education CME programs. Any aforementioned relationship that poses a potential conflict of interest will be resolved prior to publication/distribution of the CME activity, and proper notification disclosed to program participants prior to the start of the activity.

Disclosure of any off-label medication usage for indications that are not currently approved by the Federal Drug Administration discussed within the CME content will be disclosed within the lesson.

Accreditation Statement * Hatherleigh's CME Designation

The Hatherleigh Company, Ltd. designates this CME journal for a maximum of **40 AMA PRA Category 1 Credits.** Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Hatherleigh Company, Ltd. is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) by The Hatherleigh Company, Ltd.

How the Program Works * Needs Assessment * Evaluation

Directions in Psychiatry includes 78 CME questions focused on key learning points within the lessons. The answers to each question must be recorded on the supplied quiz response form or via the response form at Hatherleigh's website. All 78 questions should be answered on that form or online and submitted to Hatherleigh via the website, fax, e-mail, or regular mail for scoring. On average, participants will take up to 40 hours or more to complete this Hatherleigh CME program (i.e., reading and studying the lessons and answering the CME questions). Participants must complete and return the program assessment form which is included with each program. Participants can submit these forms with the quiz response form. Upon successful completion of the program (at least 75% correct), Hatherleigh will send participants a certificate of achievement worth 40 credit hours and a score report.

This CME program was created from a learning needs assessment of participants in previous CME programs, who are virtually all physicians and other mental health clinicians. Their expressed needs were assessed by the Medical Director, the Program Advisory Board members, and editorial staff in the development of this curriculum.

About The Hatherleigh Company, Ltd. * Contact Information

The Hatherleigh Company, Ltd. has published continuing medical education programs in psychiatry for more than 30 years. Dr. Frederic Flach, the company's founder, created *Directions in Psychiatry*, Hatherleigh's flagship CME program to ensure the presence of a truly independent and highly professional perspective on issues of immediate clinical import—ranging from pharmacotherapy to psychotherapy, from technical information to ethical priorities. We look forward to hearing from all subscribers via e-mail at: support@hatherleigh.com. For more information about Hatherleigh CME programs, visit our website at www.hatherleigh.com, or call: 1-800-367-2550.

Accreditation Standards: IOM; ACGME / ABMS Competencies

Directions in Psychiatry, Vol. 36

In accordance with accreditation guidelines set forth by the ACCME, we encourage you to review the following areas of core competency and desirable physician attributes endorsed by the *Institute of Medicine* (IOM); *The Accreditation Council for Graduate Medical Education* (ACGME) / *American Board of Medical Specialties* (ABMS). Each CME lesson in this activity addresses at least one or more of the following attributes in each of the three areas of competency as listed below.

Institute of Medicine Core Competencies:

Provide Patient-Centered Care: Identify, respect, and care about patients' differences, values, preferences, and expressed needs; relieve pain and suffering; coordinate continuous care; listen to, clearly inform, communicate with, and educate patients; share decision-making and management; and continuously advocate disease prevention, wellness, and promotion of healthy lifestyles, including a focus on population health.

Work in Interdisciplinary Teams: Cooperate, collaborate, communicate, and integrate care in teams to ensure that care is continuous and reliable.

Employ Evidence-Based Practice: Integrate best research with clinical expertise and patient values for optimum care, and participate in learning and research activities to the extent feasible.

Apply Quality Improvement: Identify errors and hazards in care; understand and implement basic safety design principles, such as standardization and simplification; continually understand and measure quality of care in terms of structure, process, and outcomes in relation to patient and community needs; and design and test interventions to change processes and systems of care, with the objective of improving quality.

Utilize Informatics: Communicate, manage, knowledge, mitigate error, and support decision-making using Information technology.

ACGME Competencies:

Patient Care that is compassionate, appropriate, and effective for the treatment of health problems and the promotion of health.

Medical Knowledge about established and evolving biomedical, clinical, and cognate (e.g. epidemiological and social-behavioral) sciences and the application of this knowledge to patient care.

Practice-Based Learning and Improvement that involves investigation and evaluation of their own patient care, appraisal and assimilation of scientific evidence, and improvements in patient care.

Interpersonal and Communication Skills that result in effective information exchange and teaming with patients, their families, and other health professionals.

Professionalism, as manifested through a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to a diverse patient population.

Systems-Based Practice, as manifested by actions that demonstrate an awareness of and responsiveness to the larger context and system of health care and the ability to effectively call on system resources to provide care that is of optimal value.

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Part I-Professional Standing: Medical specialists must hold a valid, unrestricted medical license in at least one state or jurisdiction in the USA, its territories or Canada.

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Part III-Cognitive Expertise: They demonstrate, through formalized examination, that they have the fundamental, practice-related and practice environment-related knowledge to provide quality care in their specialty.

Part IV-Practice Performance Assessment: They are evaluated in their clinical practice according to specialty-specific standards for patient care. They are asked to demonstrate that they can assess the quality of care they provide compared to peers and national benchmarks and then apply the best evidence or consensus recommendations to improve that care using follow-up assessments.

Directions in Psychiatry, Vol. 36 * Part 1

IOM Core Competencies	Lesson 1	Lesson 2	Lesson 3	Lesson 4	Lesson 5
Provide patient-centered care	X			X	
Work in interdisciplinary teams				X	
Employ evidence-base practice		X	X		X
Apply quality improvement		X			
Utilize informatics		X			X
ACGME Competencies					
Patient care	X		X	X	
Medical knowledge	X	X	X	X	X
Practice-based learning and improvement	X				X
Interpersonal and communication skills					
Professionalism				X	
System-based practice		X			
ABMS MOC Competencies					
Professional standing					
Commitment to lifelong learning	X		X		
Cognitive expertise		X			
Performance in practice	X		X		

Accreditation Standards: IOM; ACGME / ABMS Competencies

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Directions in Psychiatry, Vol. 36 * Part 2					
IOM Core Competencies	**Lesson 6**	**Lesson 7**	**Lesson 8**	**Lesson 9**	**Lesson 10**
Provide patient-centered care	X	X		X	
Work in interdisciplinary teams		X		X	
Employ evidence-base practice			X		X
Apply quality improvement				X	
Utilize informatics					
ACGME Competencies					
Patient care	X	X	X	X	
Medical knowledge	X	X	X	X	X
Practice-based learning and improvement					
Interpersonal and communication skills	X				
Professionalism					
System-based practice					
ABMS MOC Competencies					
Professional standing					
Commitment to lifelong learning	X	X	X	X	
Cognitive expertise					X
Performance in practice					

Accreditation Standards: IOM; ACGME / ABMS Competencies

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Directions in Psychiatry, Vol. 36 * Part 3					
IOM Core Competencies	**Lesson 11**	**Lesson 12**	**Lesson 13**	**Lesson 14**	**Lesson 15**
Provide patient-centered care		X	X	X	X
Work in interdisciplinary teams					
Employ evidence-base practice	X			X	
Apply quality improvement					X
Utilize informatics					
ACGME Competencies					
Patient care		X	X	X	X
Medical knowledge	X		X	X	X
Practice-based learning and improvement		X	X		
Interpersonal and communication skills	X				
Professionalism	X				
System-based practice					X
ABMS MOC Competencies					
Professional standing					
Commitment to lifelong learning	X	X	X	X	
Cognitive expertise				X	X
Performance in practice	X		X	X	

Accreditation Standards: IOM; ACGME / ABMS Competencies

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Apply Quality Improvement: Identify errors and hazards in care; understand and implement basic safety design principles, such as standardization and simplification; continually understand and measure quality of care in terms of structure, process, and outcomes in relation to patient and community needs; and design and test interventions to change processes and systems of care, with the objective of improving quality.

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Part III-Assessment of knowledge and cognitive Expertise: They demonstrate, through formalized examination, that they have the fundamental, practice-related and practice environment-related knowledge to provide quality care in their specialty.

Part IV-Improvement in performance and practice: They are evaluated in their clinical practice according to specialty-specific standards for patient care. They are asked to demonstrate that they can assess the quality of care they provide compared to peers and national benchmarks and then apply the best evidence or consensus recommendations to improve that care using follow-up assessment.

Directions in Psychiatry, Vol. 36 * Part 4					
IOM Core Competencies	**Lesson 16**	**Lesson 17**	**Lesson 18**	**Lesson 19**	**Lesson 20**
Provide patient-centered care	X	X			
Work in interdisciplinary teams				X	X
Employ evidence-base practice				X	
Apply quality improvement			X	X	X
Utilize informatics			X		X
ACGME Competencies					
Patient care	X	X			
Medical knowledge	X		X	X	X
Practice-based learning and improvement		X			
Interpersonal and communication skills	X				
Professionalism					
System-based practice			X	X	X
ABMS MOC Competencies					
Professionalism and professional standing					
Commitment to lifelong learning and self-assessment	X	X		X	
Assessment of knowledge, judgment, skills, cognitive expertise			X		X
Improvement in performance and medical practice					

Conflict of Interest Faculty/Board Disclosures

The authors of the lessons in this CME program are paid an honorarium to produce original manuscripts on the invited topics. The authors were selected for their expertise and, most often, on the strength of presentations made on those topics in previously published papers or symposia. Relationships are disclosed below, if they exist, between the *Directions in Psychiatry* faculty and their immediate family members, and commercial and/or pharmaceutical companies below. Disclosure of off-label medication usage for indications that are not approved by the FDA will be disclosed on the title page of each lesson.

No commercial support was used in the development of the enclosed CME lessons.

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Alison Heru, MD: Dr. Heru has no conflicting interests to disclose.

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George I. Papakostas, MD: Dr. Papakostas has no conflicting interests to disclose.

Hatherleigh Editorial Staff:

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Stacy M. Powell, Managing Editor: Ms. Powell has no conflicting interests to disclose.

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Directions in Psychiatry

Breakdown of Tested Areas for Volume 36

In an effort to help program participants determine their personal learning plans and address any gaps in their knowledge, every volume of *Directions in Psychiatry* presents lesson categorized into tested areas, listed below. To determine your score in any tested area, review the answer sheet included with your certificate. Add your correct answers for the questions listed in each tested area, and compare it to the total possible number of correct answers, listed next to each tested area. Below is an example.

	Question	Your response	Correct response	You received
	1	D	⟹ A	
Less 1	2	B	B	¾
Questions	3	C	C	3 out of 4 questions correct for the

Topic Areas/ Lesson numbers & possible questions correct.		Topic Areas/ Lesson numbers & possible questions correct.	
Addictions: Lessons: 2, 3, 8, 9, 19	ˣ/20	**Mood Disorders:** Lessons: 1, 3, 4, 5, 19	ˣ/20
Anxiety Disorders: Lessons: 1, 3, 5, 6, 7, 15, 16, 17	ˣ/32	**Neurobiology:** Lessons: 2, 13, 14, 16, 18	ˣ/20
Child/Pediatric, Adolescent Psychiatry: Lessons: 1, 2, 7, 9, 13, 14, 19, 20	ˣ/32	**Pain/Palliative Care:** Lesson: 3, 7, 17	ˣ/12
Cognitive Disorders: Lesson: 1, 3, 7, 12, 13, 17, 18, 19	ˣ/32	**Personality Disorders:** Lessons: 5	ˣ/4
Cultural Psychiatry: Lesson: 6	ˣ/4	**Professional Standards:** Lessons: 9, 11	ˣ/8
Developmental Disorders: Lessons: 13, 14, 19, 20	ˣ/16	**Psychopharmacology:** Lessons: 1, 2, 3, 6, 7, 8, 9, 13, 14, 19	ˣ/40
Dissociative Disorders: Lessons: 15	ˣ/4	**Psychotic Disorders:** Lessons: 5, 8, 15	ˣ/12
Domestic Violence: Lessons: 19	ˣ/4	**Psychosocial Treatment / Psychotherapy** Lessons: 3, 7, 10, 14, 17	ˣ/20
Eating Disorders: Lessons: 10	ˣ/4	**PTSD/Trauma/Disaster Psychiatry:** Lessons: 1, 5, 6, 7, 12, 16	ˣ/24
Ethical Issues: Lesson: 4	ˣ/4	**Sexual Disorders: Gender, Paraphilia, Dysfunction:** Lessons: 1	ˣ/4
Family Psychiatry: Lesson: 2, 3	ˣ/8	**Sleep Disorders:** Lesson: 7	ˣ/4
Geriatrics: Lessons: NA	ˣ/0	**Somatoform Disorders:** Lessons: 3	ˣ/4
HIV/AIDS/Infectious Disease: Lessons: 9	ˣ/4	**Suicide & Suicide Prevention:** Lessons: 3, 6	ˣ/8
Impulse Control Disorders: Lesson: NA	ˣ/0	**Technology in Psychiatry:** Lesson: 16	ˣ/4
Malpractice Risk/Forensics: Lessons: 11	ˣ/4	**Women's Issues:** Lesson: 19	ˣ/4
Medical Errors: Lessons: 15	ˣ/4	**Other Clinical Issues:** Lessons: NA	ˣ/0

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PTSD: Overview and DSM-5 Changes

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KEY WORDS: PTSD • Trauma • DSM-IV-TR • DSM-5 criteria • Pharmacological treatment

LEARNING OBJECTIVES: This lesson will: (1) enable clinicians to understand the history behind the conceptualization of PTSD and learn the factors that influenced the changes in its criteria over time; (2) provide them with an update on the current DSM-5 criteria for diagnosis and how they differ from those of the DSM-IV-TR; (3) review the risk factors, presentation, and pathophysiological changes associated with the condition; and (4) allow them to understand the pharmacological and non-pharmacological treatment modalities recommended.

LESSON ABSTRACT: The diagnosis of *Posttraumatic Stress Disorder* (PTSD) was included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) for the first time in 1980. The release of the new criteria for the diagnosis of PTSD in the 5th Edition (DSM-5) in 2013 is the second major revision of the requirements for diagnosis since then. PTSD has been the most common psychiatric diagnosis influenced by social and political forces, with a large number of social and scientific misconceptions. This revision came as a result of a major increase in the research about the demographics of PTSD. More recently, several studies have increased our understanding of the biological factors that affect PTSD patients and will hopefully enhance treatment outcomes. This lesson will give an overview of PTSD in terms of its history, presentation, and treatment and explain the recent changes in the diagnostic criteria.

COMPETENCY AREAS: This lesson will enable clinicians to treat and recognize the differences in the diagnosis of PTSD between the DSM-IV-TR and the DSM-5. Further, readers will review basic concepts and risk factors related to PTSD, differences between men, women, and children in its presentation, and the pharmacological and non-pharmacological management of PTSD.

Introduction

The term *posttraumatic stress disorder* (PTSD) was introduced in the *Diagnostic and Statistical Manual of Mental Disorders,* 3rd *edition* (DSM-III) in 1980[1] in response to the experiences of many patients, foremost among them Vietnam War veterans. Due to its association with the war in Vietnam, PTSD has become synonymous with many historical wartime diagnoses such as railway spine, stress syndrome, nostalgia, soldier's heart, shell shock, battle fatigue, combat stress reaction, or traumatic war neurosis.[2] However, soldiers are not the only vulnerable group; any traumatic event (from sexual assault, child abuse, and elder abuse to extreme weather events and urban violence) can place an individual at risk for PTSD, regardless of age, biological sex, or cultural background.[3] Most people will experience at least one traumatic event during their lifetime. **In the United States, about 90% of individuals will experience one or more traumatic events during their lifetimes,[4] and yet the lifetime prevalence of PTSD among adult Americans is estimated to be 6.8%.[5]** The global estimated lifetime prevalence of PTSD is approximately 4%, ranging from 1.3% in Japan to 8.8% in Northern Ireland.[6, 7]

When looking at the history of posttraumatic stress, one cannot help but notice how the cultural, political, and legal forces shaped the definition of the condition and its perception both in society as a whole and among the medical establishment. In the early twentieth century during the two world wars, the condition was associated with negatively labeling patients as being either soft-hearted whiners or malingerers and profit seekers. As a great majority of the patients were soldiers (due to the nature and severity of war trauma), military establishments looked at posttraumatic stress with skepticism because it undermined manpower and recruitment. When a framework was finally established in the 1980s, the DSM-III defined the nature of the traumatic event as a "catastrophic stressor that is outside the range of usual human experience"[1] with the goal being to overcome the military and societal labeling of PTSD patients as having a weakness of character, thus implying unintentionally that the condition is a normal reaction to abnormal circumstances. However, the condition is neither normal nor inevitable in the wake of catastrophe.[8] After the war in Vietnam ended, researchers discovered that civilian trauma can also cause PTSD. In fact, women and younger people appear to be more vulnerable to PTSD.[9, 10] Hence, the focus of the DSM-III on the nature of the trauma was perceived by a majority as narrow and denied many patients appropriate care and compensation.[11]

The DSM-IV in 1994 and its text revision (DSM-IV-TR) in 2000 gave a more comprehensive definition to the traumatic stressor but added the following: "The person's response to the event must involve intense fear, helplessness, or horror."[12] This criterion ignored the individuality of patients, and the possibility that not all people respond in the same time frame and with the same response. **The recent publication of the DSM-5 in 2013[13] included a considerable revision of the PTSD diagnosis, as PTSD was removed from the anxiety disorders chapter and put in a special chapter for trauma- and stressor-related disorders, which includes reactive attachment disorder, disinhibited social engagement disorder, acute stress disorder, and adjustment disorders.** In doing this, the DSM-5 recognizes the heterogeneity of individual responses to stress with either internalization or externalization and the possibility of the presence of elements of any of the anxiety reactions to stress throughout the course of the individual's life and the course of the reaction itself. Moreover, criterion A2 (subjective reaction) has been eliminated. Whereas there were 3 major symptom clusters in the DSM-IV-TR, there are now 4 symptom clusters in the DSM-5. Criterion B did not change, but Criterion C now only contains avoidance and Criterion D still retains most of the DSM-IV-TR numbing symptoms but now also includes new or reconceptualized symptoms. Table (1) explains the differences between the criteria of PTSD in the DSM-IV-TR and the DSM-5. It was projected that these revisions will lower the prevalence of PTSD.**[14]**

In fact, one recent study found that refugees with trauma were less likely to be diagnosed with PTSD using DSM-5 (49.3%) than when using DSM-IV-TR (60.4%) ($p < .001$).[15]

Diagnosis and DSM-5 Criteria

In adults, PTSD is a condition that develops after exposure to an emotionally traumatic event (Criterion A). The event is described as an actual or threatened death, serious injury, or sexual violence, and the exposure can take one of 4 forms: (A) direct exposure to the event; (B) witness to the exposure of others; (C) learning about the

Table 1:
PTSD in the DSM-IV-TR and the DSM-5

DSM-IV-TR	DSM-5
PTSD is part of the Anxiety Disorders Chapter	Part of the Trauma and Stress-Related Disorders Chapter
6 Criteria; A to F	8 Criteria in the 2015 edition; A to H

Criterion A: Trauma
 	
    A1: Exposure is limited to 3 ways; personal experience, or witnessing, or learning about trauma of close others.
 	
    A2: The person's response to the event must involve intense fear, helplessness, or horror (or in children, the response must involve disorganized or agitated behavior)
	Criterion A: Trauma
	· Exposure the same 3 ways as DSM-IV-TR and added a fourth way which is; experiencing repeated or extreme exposure to aversive details of the traumatic event(s)
	· Subjective reaction; A2 in DSM-IV-TR was removed

Criterion C: Persistent avoidance and numbing · Sub-criteria C1 and C2 are for avoidance · Sub-criteria C3 to C7 are for numbing symptoms, equivalent to some of sub-criteria D in DSM-5	Criterion C: Persistent avoidance · Two sub-criteria for avoidance only
Criterion D: Persistent arousal · 5 sub-criteria D1 to D5 · Equivalent to some of sub-criteria E in DSM-5	Criterion D: Alterations in cognitions and mood · 7 sub-criteria D1 to D7 · Sub-criteria D1 and D5 to D7 are equivalent to C3 to C6, which are referred to as numbing symptoms in DSM-IV-TR · C7; Sense of a foreshortened future, was removed in DSM-5 · D2; Exaggerated negative beliefs about oneself and others, D3; Distorted blame of himself/herself or others, and D4; Persistent negative emotional state, are new criteria in DSM-5
	· Criterion E: Alterations in arousal and reactivity · 6 sub-criteria E1 to E6 · Sub-criteria E1 and E3 to E6 are equivalent to sub-criteria D in DSM-IV-TR · Sub-criterion E2; Reckless or self-destructive behavior, is new in DSM-5
· Criterion B is equivalent in both editions · Criteria E and F in DSM-IV-TR are equivalent to criteria F and G in DSM-5 respectively · New to DSM-5 2015 edition: criterion H; the symptoms are not attributable to the physiological effects of a substance or another medical condition	

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision;
DSM-5: Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition; PTSD: Posttraumatic Stress Disorder.

exposure of a close family member or a close friend; (D) repetitive experiencing of the consequences or the details of events happening to unrelated others, as in the course of investigating a crime for rescue workers or other first responders. As a direct consequence of the exposure, there are 4 clusters of symptoms and 3 conditions that have to be fulfilled for a diagnosis of PTSD to be made according to the DSM-5, and these are: Criterion B—One or more of these intrusion symptoms: recurrent distressing memories or dreams; dissociative reactions where the patient relives the events (called "flashbacks)"; or intense or prolonged psychological or physiological distress upon exposure to cues (external or internal) that resemble the traumatic event. Criterion C—includes One or more

of these avoidance symptoms: avoidance of memories, thoughts, or feelings; and/or avoidance of people, places, or activities related to the event. Criterion D—includes Alteration of cognition and mood due to the event must be evidenced by 2 or more of the following symptoms: pervasive negative cognitive and emotional reactions to the event, such as memory gaps and distortions in the causes or consequences of the event leading to unsubstantiated blame for self or others or leading to distrust for others and a pervasive negative emotional state, or inability to attain a positive emotional state; and/or decreased interest in activities, or estrangement from others. Finally, Criterion E—includes the presence of 2 or more altered arousal and reactivity reactions, such as: an increase in irritability, anger, and aggression to others or in the form of reckless or self-destructive behavior; hypervigilance; restless sleep; difficulty concentrating; or exaggerated startle reflex. The symptoms have to be present for more than one month and cause clinically significant distress or impairment, and cannot be explained by other medical conditions or substance use.

In children older than 6 years, the criteria are the same as adults; however, for the first time, the DSM-5 places children under 6 years old as a population group that is susceptible to PTSD with certain guidelines that apply only to them: (A) the traumatic experience is similar to adults but without the repetitive experiencing form of exposure; (B) the intrusive symptoms can be expressed through repetitive play that bear elements of the trauma, and the distressful dreams do not have to have a specific content related to the trauma; (C) the avoidance and altered cognition symptoms are bundled together in one cluster and only one symptom is sufficient for diagnosis from six years old that are similar to adult symptoms, except there are no "memory gaps," misplaced blame, or distrust for others; (D) the altered arousal cluster is without reckless/self-destructive behavior.

Presentation

There are 2 subcategories of PTSD that should be specified according to the DSM-5 guidelines. PTSD with dissociative symptoms refers to alterations in consciousness, identity, and memory, which can manifest as either *depersonalization*, which refers to feelings of being an outside observer of or detached from oneself, or *derealization*, which refers to an **experience of unreality, distance, or distortion.** PTSD with delayed expression refers to a full PTSD diagnosis not being met until at least 6 months after the trauma(s). Most often people who experience what is sometimes also termed delayed-onset PTSD do indeed suffer from sub-threshold symptoms well before 6 months after the traumatic event; in these cases most will meet the criteria for Acute Stress Disorder, but over time the burden of symptoms increases[16] as the individual fails to get sufficient support or effectively re-establish their pre-trauma routine. In other cases, individuals cope with the psychological consequences of the traumatic event well, but a subsequent significant life event (e.g., relationship breakdown) occurs and the individual may attribute the subsequent distress to the earlier trauma rather than the more recent life event.

The initial phases of PTSD are usually predominated by the intrusion and altered arousal symptoms, while the avoidance and the altered cognition and negative emotions are more prominent in the chronic phases of the disease. There are differences between men and women in the presentation of PTSD. The major differences in prevalence[9,17] and presentation[18-20] between men, women, and children are listed in Table (2). There is a linear correlation between the severity and chronicity of trauma and the severity and chronicity of PTSD.[21] Between 30% and 50% of people will have a chronic course to their illness. People who suffer from chronic intentional trauma over a long period of time and starting early in life develop an informal category of PTSD termed *Complex PTSD*. Complex PTSD is characterized by a poor self-image, disturbed interpersonal relations, frequent dissociative symptoms, somatization, and defective belief systems. Complex PTSD can be challenging to treat, and the treatment goal is to restore the victim's individuality and control.[22]

PTSD is rarely presented as an isolated condition. Mood disorders, anxiety disorders, chronic pain, and substance misuse frequently coexist. Because of this high comorbidity, it is important to recognize potentially treatable medical contributors to posttraumatic symptomatology, particularly *traumatic brain injury* (TBI), psychoactive substance use disorders, and pain. Usually a careful history and physical examination are sufficient tools for differential diagnosis, paying special attention to re-experiencing and avoidance symptoms, which are unique to PTSD.

Table 2:
Differences in PTSD Between Men, Women, and Children

	Men	**Women**	**Children**
Type of trauma	Combat-related violence	Sexual violence	Abuse (physical and sexual), disruption of family and social support (as in natural and man-made disasters)
Lifetime Prevalence	3.6%	9.7%	5%
Symptoms	Irritability and impulsiveness	Numbing and avoidance	Time skew* and Omen formation**
Course	Less chronic	Chronic	Long-term abuse causes chronic PTSD
Comorbidity	Substance use disorders	Mood and anxiety disorders	Varies with age

*   Time skew refers to a child mis-sequencing trauma-related events when recalling memories.
** Omen formation is a belief that there were warning signs that predicted the trauma; children often believe that if they are alert enough, they will recognize warning signs and avoid future traumas.

PTSD is associated with numerous adverse health and social consequences, including higher rates of diabetes, cardiovascular disease, autoimmune diseases, hypertension, and dementia, as well as increased rates of psychiatric hospitalization, unemployment, poverty, and suicide.[23]

Risk Factors

Risk factors to exposure to trauma include: less than a college education, male gender, childhood conduct problems, a family history of psychiatric illness, and extroverted and neurotic personalities. Among those exposed to trauma, the risk factors for developing PTSD include female gender, low social support, a low *Intelligence Quotient* (IQ), a pre-existing psychiatric illness, and a family history of mood disorders, anxiety, or substance abuse.[24] A recent body of studies has established the presence of physiological, anatomical, and genetic changes that are associated with PTSD. A few changes precede trauma and thus are considered risk factors, while a few others are considered sequelae to PTSD, but the majority of changes have not been extensively studied to ascertain whether they are a cause or effect. Most of these changes are not unique to PTSD, but rather are related to the symptomatology of PTSD.

To further understand those changes, one must understand the physiology of stress. Stress normally initiates the *autonomic nervous system* (ANS) and limbic system. Activation of these systems by a "fight or flight" situation results in an increased release of norepinephrine, which then elicits increased heart rate, respirations, and alertness to help deal with the perceived stressor. This is followed by a response from the *hypothalamic-pituitary-adrenal* (HPA) axis, with its multiple feedback loops, that restores homeostasis.[25] PTSD causes the patient to continue to re-experience the traumatic events, which, in turn, causes heightened vigilance and overuse of these normal stress responses and eventually certain changes in the endocrine and neuroendocrine systems, as well as the neuroimaging studies of PTSD patients.

Endocrine and Neuroendocrine Changes:

Recent studies have suggested that early-life stressors cause neuroendocrine changes that affect stress reactivity, as measured by the HPA axis and ANS activation.[26] Women are more likely than men to develop PTSD, which may be in part because fluctuating levels of ovarian hormones are correlated positively with anxious responses to stress.[27] However, increased oxytocin levels may decrease the risk of stress-related psychopathology.[28]

PTSD patients exhibit increased levels of norepinephrine, *corticotropin-releasing hormone* (CRH), and proinflammatory cytokines, reflecting reduced glucocorticoid signaling. PTSD observations differ from those observed in studies of acute and chronic stress and *major depressive disorder* (MDD), as low cortisol levels are

seen.[29] Emerging research indicates that these alterations may instead reflect pre-traumatic vulnerabilities to the later development of PTSD,[30] or this profile can also be explained by the fact that MDD and PTSD coexist in a significant proportion of patients.[31]

Neuroimaging Changes:

The brain regions related to symptoms of the disorder include the hippocampus, amygdala, ventromedial prefrontal cortex, dorsal anterior cingulate cortex, and insular cortex. *Structural magnetic resonance imaging* (sMRI) studies have shown a decrease in the volume of these structures with the exception of the amygdala in patients with PTSD.[32-37] These changes are most significant in the subfields of the hippocampus with the greatest concentration of glucocorticoid receptors (i.e., CA3/dentate gyrus). Corticosteroids may impair neurogenesis, decrease dendritic branching, and potentiate the excitotoxic effect of glutamate neurotransmission.[33] More importantly, these hippocampal changes are associated with memory deficits, which are the most frequent cognitive alterations observed among patients with PTSD.[38] It is not clear if the changes to the hippocampal volume is caused by the trauma or simply represents a risk factor.[39-41]

Pharmacological Treatment of PTSD

Most clinical practice guidelines recommend medication as a first-line treatment for PTSD.[42] In the past several years, there have been many advances in the pharmacotherapeutic approach to PTSD. **The *Food and Drug Administration* (FDA) has approved both *sertraline* (Zoloft) and *paroxetine* (Paxil), both *selective serotonin reuptake inhibitors* (SSRIs), for the treatment of PTSD. Although the literature points to key biological systems involved in PTSD, there have been no new FDA-approved medications for 10 years.[42]** Medications affecting serotonergic, noradrenergic, dopaminergic, and GABAergic systems have been studied in PTSD.

SSRIs remain the mainstay pharmacological treatment for PTSD based on 4 clinical practice guidelines,[42] with 4 out of 6 recommending SSRIs as the first-line monotherapy for PTSD.[43-46] Compared to placebos, both sertraline and paroxetine reduce PTSD symptoms and lead to remission in about 30% of patients.[47] When treatment is extended, remission rates increase. Sertraline treatment extended from 12 to 36 weeks resulted in remission rates increasing from 30% to 55%.[47] Similarly, the discontinuation of SSRI results in a return of PTSD symptoms. In their review of 12 *randomized-controlled trials* (RCTs) on SSRIs, Cochrane and other reviews found paroxetine, sertraline, and *fluoxetine* (Prozac) all superior to a placebo.[42] SSRIs reduce the core PTSD symptoms of re-experiencing, avoidance, numbing, and hyperarousal. Neurogenesis may also increase the treatment response in PTSD; one 9–12 month open-label clinical trial found that patients treated with paroxetine had a 4.66% increase in mean hippocampal volume on MRI, leading to improved declarative memory and fewer PTSD symptoms.[48]

Serotonin-norepinephrine reuptake inhibitors (SNRIs) have been studied in the treatment of PTSD. Two studies of 6- or 12-month treatment with *venlafaxine XR* (Effexor XR) showed superiority to a placebo.[49] Venlafaxine XR is thought to increase one's ability to deal with stress, and long-term effects are believed to be similar to SSRI treatment, with an approximately 30% remission rate after 12 weeks of treatment.[42]

Other antidepressants have also been studied. Agents with both serotonergic and adrenergic activity, such as *mirtazpine* (Remeron), have been studied for use as a PTSD monotherapy. Currently, mirtazapine is recommended as a second-line agent.[50] *Trazodone* (Oleptro) exerts effects through increasing serotonergic activity, and the blockage of postsynaptic 5HT2 receptors has limited efficacy as a monotherapy for PTSD. As trazodone is sedating, it is often used in addition to SSRIs for insomnia.[42] *Bupropion* (Wellbutrin, Zyban) acts by increasing both noradrenergic and dopaminergic activities. RCTs do not provide evidence for using bupropion as evidence-based treatment for PTSD.[42]

Adrenergic dysregulation is commonly seen in PTSD.[42] *Prazosin* (Minipress), as an α1-adrenergic antagonist, decreases traumatic nightmares.[51,52] Unfortunately, there are mixed results for using prazosin to target other symptoms of PTSD, possibly due to prazosin's short half-life. One recent study showed twice daily dosing of prazosin was indeed effective for reducing overall PTSD symptoms.[53] At this time, the VA/DoD clinical practice guidelines recommend prazosin as an

Table 3:
Pharmacotherapy for PTSD

Commonly Prescribed Medications for PTSD					
Name	**Drug Class**	**FDA approval**	**Dose range**	**Goal of Treatment**	**Common Side Effects**
Paroxetine (Paxil, Pexeva) Sertraline (Zoloft) Fluoxetine (Prozac; Sarafem) Citalopram (Celexa) Escitalopram (Lexapro)	SSRIs [a]	Yes Yes No No No	20–60 mg/day 25–200 mg/day 20–80 mg/day 20–40 mg/day 10–20 mg/day	Overall reduction of PTSD symptoms	Sexual dysfunction Sedation Appetite change Headache
Venlafaxine (Effexor) Desvenlafaxine (Pristiq) Duloxetine (Cymbalta)	SNRIs	No No No	75–300 mg/day 50–100 mg/day 30–120 mg/day	Overall reduction of PTSD symptoms	GI upset Sexual dysfunction Elevated BP
Mirtazapine [b] (Remeron, Remeronsoltab) Trazodone [c] (Oleptro)	Adrenergic-Serotonergic	No No	15–45 mg/day 50–200 mg/day	Overall reduction of PTSD symptoms	Weight gain Sedation
Prazosin (Minipress)	Alpha-1-receptor Antagonist	No	1–10 mg/day	Nightmares	Orthostatic hypotension Dizziness
Propranolol (Inderal, Hemangeol)	Beta-adrenergic Antagonist	No	40 mg TID x 7–10 days	Prevention of future symptoms	Bradycardia Dizziness Hypotension
Topiramate (Topamax, Qudexy)	Anticonvulsants	No	25–400 mg/day	Anxiolytic, antikindling	GI upset Cognitive slowing Kidney stones
Risperidone (Risperdal)	Atypical Antipsychotics	No	0.25–2 mg/day	Best with comorbid psychosis	Neurological (dystonia, EPS, NMS, akathisia) Metabolic syndrome

SSRI = Selective Serotonin Reuptake Inhibitor,
SNRI = Serotonin Norepinephrine Reuptake Inhibitor
[a] First-line monotherapy; [b] Second-line monotherapy; [c] limited efficacy as monotherapy

evidence-based treatment for nightmares, but no other PTSD symptoms.[54] Beta-adrenergic antagonists, such as *propranolol* (Inderal, Hemangeol), show mixed results in the treatment of PTSD. Monotherapy with propranolol has been promising for disrupting the reconsolidation of traumatic memories[42] and decreasing intrusive thoughts and reactivity.[55] Alpha-2-adrenergic agents, such as *clonidine* (Catapres, Kapvay), and *guanfacine* (Tenex, Intuniv), show disappointing or even negative results.[56]

GABAergic agonists, such as benzodiazepines which act on GABA-A receptors, are not recommended for PTSD as per most clinical practice guidelines.[42] Similarly, benzodiazepines have not been shown effective if given prophylactically in the later development of PTSD.[57] Not only is there a lack of efficacy, but there are also commonly cited risks of dependence, falls, and cognitive dysfunction, all of which can interfere with the psycho-therapeutic treatment of PTSD.

Anticonvulsants are of interest due to their antikindling action and impact on both the glutamate and GABA systems. Unfortunately, except for *topiramate* (Topamax, Qudexy), RCT findings are disappointing. Topiramate was studied as a monotherapy for PTSD in 3 RCTs and found to reduce PTSD symptoms broadly. The *Agency for Healthcare Research and Quality* (AHRQ) stated topiramate was as effective as paroxetine or venlafaxine XR.[58] One would expect that another anticonvulsant with a similar mechanism of action of minimizing glutaminergic activity and enhancing GABAergic systems would be effective for PTSD; therefore, it remains unclear why equivocal or negative results are found in RCTs with the treatment of valproate acid, lamotrigine, and tiagabine.[42]

Atypical antipsychotics have been used as adjunctive treatment to antidepressants in partial responders. Initially, studies showed that atypical antipsychotics improved outcomes that had not improved with antidepressants, but one large multisite RCT showed that *risperidone* (Risperdal) was equal to placebo augmentation.[59] In 2010, the VA/DoD PTSD clinical practice guidelines for PTSD without psychotic features were changed from recommending risperidone augmentation to now stating that evidence is inconclusive regarding the adjunctive use of any other atypical antipsychotic.[59] Atypical antipsychotics are not recommended for PTSD monotherapy.[50] However, they are used for co-occurring psychotic symptoms and may be more helpful with psychosis than the actual PTSD symptoms.[60] Clinical practice guidelines therefore state that atypical agents can be used for co-occurring psychosis, but not for PTSD. Table (3) lists a summary of the important pharmacotherapeutic agents used in the treatment of PTSD.

Non-Pharmacological Treatment of PTSD:

While treating PTSD with pharmacotherapy has support, the *Institute of Medicine* (IOM) rates trauma-focused *cognitive-behavioral therapy* (CBT) as the only first-line treatment for PTSD,[61] with one review of 26 modalities of PTSD psychotherapies showing the strongest support for trauma-focused CBT.[62] Trauma-focused CBT includes exposure therapy, *cognitive processing therapy* (CPT), *eye-movement desensitization and reprocessing* (EMDR), and stress inoculation training.[61]

The aim of CBT is to confront traumatic memories and change maladaptive thought patterns that reinforce continual avoidance of the trauma.[61] Exposure therapy aims for the patient to experience a decrease in fear of the trauma and increase in control over their reaction to the trauma through repeated exposure to aspects of the trauma via both imaginal and in vivo exposures in a safe environment[61] coupled with processing, psychoeducation, and breathing relaxation. Exposure therapy is recommended by the IOM based on a review of 90 RCTs for PTSD.[63] CPT works to change a patient's negative thought processes related to trauma via exposure in the form of writing a narrative to help the patient identify and reshape their cognitions.[64] CPT is as efficacious as exposure therapy and has the benefit of being applicable in a variety of settings, and is used widely in the VA Healthcare system.[61] EMDR contains both elements of exposure and cognitive therapy but with additional bilateral stimulation in the form of saccadic eye movements (with an ongoing debate about the efficacy of eye movements). The majority of treatment guidelines recommend EMDR as the first-line treatment, but the IOM and American Psychiatric Association do not due to the lack of adequate evidence.[65]

Other therapies, such as psychodynamic and hypnosis, lack evidence to recommend them for the treatment of PTSD,[61] while treatment approaches such as *acceptance and commitment therapy* (ACT), *dialectical behavior therapy* (DBT) and *skills training in affective and interpersonal regulation* (STAIR) show positive findings, but only ACT and DBT have positive findings from case studies and STAIR has positive findings from one clinical trial.[61] These newer treatments do show hope, but require more evidence to recommend their use for the treatment of PTSD.

Adult PTSD Case Vignette:

Ms. Santoro is a 43-year-old Hispanic woman with a history of MDD who presented to establish care with a psychiatrist after her therapist (who also prescribed medication and with whom she had been working with for the past 5 years) moved away. She presented to the clinic stating that she needed assistance in the form of both medication management and therapy for depression. Ms. Santoro's medical history was

significant for morbid obesity (BMI of 54), migraines, type 2 diabetes mellitus, obstructive sleep apnea, post-herpetic neuralgia, hypertension, asthma, and hyperlipidemia. She had been prescribed *carbamazepine* (Tegretol XR) 400 mg twice daily for post-herpetic neuralgia, *amitriptyline* (Vanatrip, Elavil) 25 mg at bedtime for migraines, trazodone 150 mg at bedtime for sleep, and venlafaxine XR 300 mg daily for depression. She had been on this medication regimen, unchanged, for approximately 6 years.

Ms. Santoro described depression beginning at 10 years old as a result of trauma. She was visiting her paternal uncle with her parents in Honduras when he sexually assaulted her. She was sleeping in a room there; he entered late at night, vaginally penetrated her, smothered her with a pillow during the attack, and then threatened to kill her brother if she told anyone. At 21 years old, Ms. Santoro disclosed the abuse to her parents. Her mother was very supportive, while her father never discussed the abuse. However, her family has not had any contact with the uncle since.

She believed the abuse had shaped her entire life. She remembered being an outgoing and happy child, well-liked by everyone around her. After the abuse, she sunk into depression and became anxious and isolated. She experienced regular nightmares of being smothered, trapped, and unable to escape and breathe. Thus, she was never able to tolerate the use of a CPAP machine for sleep apnea. During a comprehensive psychiatric assessment, Ms. Santoro disclosed avoiding thinking about the abuse, complete social isolation due to lack of trust, the avoidance of any physical intimacy and no history of physical intimacy, guilt about her role in the abuse (she felt she somehow enticed her uncle into abusing her), hyperarousal where she always made sure to position herself by an exit, and self-sabotage with excessive food in the hopes her obesity would fend off predators.

After attending 2 years of community college, Ms. Santoro took a job working in the cafeteria in food services for her local area elementary school. She had steady employment there. She has never lived on her own; she is still living with her parents, with whom she gets along with well. She does not have any substance use.

On mental status exam, findings were significant for morbid obesity, hypervigilance (she made sure to position herself in the room so that she knew clearly where the exit door was located), extremely tearful affect throughout, and hyperventilation to the point of terminating the interview when discussing sexual assault. During her initial visit, amitriptyline was increased to 100 mg at bedtime, and prazosin 2 mg at bedtime was added for nightmares. On the next visit, Ms. Santoro noted improvements in her anxiety and better sleep, stating that she now felt like "an observer rather than an active participant" in her dreams.

Based on the presentation of this case and considering pharmacotherapy of PTSD, any of the following approaches would be effective management of this case:

1. Add an SSRI, as SSRIs are recommended as first-line monotherapy for PTSD[2-5] with FDA approval for both sertraline and paroxetine.

2. Although SSRIs remain the main treatment of choice for PTSD, one could also use SNRIs, as studies have shown venlafaxine XR superior to a placebo.[8]

3. Trazodone has limited efficacy for PTSD monotherapy, but is often used in addition to SSRIs for insomnia.

4. Continue and maximize dose of prazosin for the treatment of PTSD-related nightmares.

5. Consider the use of topiramate, as this has been shown effective for the reduction of PTSD symptoms.[4]

Child PTSD Case Vignette:

Mr. Ashby is a 5-year-old Caucasian boy who came into the child psychiatry clinic to establish care at the recommendation of school counselors. He presented with his paternal grandfather, who is the boy's legal

guardian. His grandfather stated that Mr. Ashby had been through a tumultuous first 5 years of his life and there were concerns about his level of functioning in school, given his background.

Mr. Ashby was raised by his biological mother along with his sister, who is 2 years older than he is. His father was never involved due to poorly controlled bipolar disorder and substance use. At 2 years old, the patient was found blue at the bottom of a swimming pool and was revived. Later that year, he ingested a handful of his mother's epilepsy medication pills, resulting in hospitalization. Medical opinion was that both incidents had caused brain injury. *Child Protective Services* (CPS) intervened 2 years later when a television fell on him and he was found to be eating feces. He was placed in multiple different foster care homes as his biological mother would seek custody again, which she would only sustain for a short period of time. Although his mother had men in and out of their home life and his sister was sexually abused, Mr. Ashby denied sexual abuse himself. Given his unstable living situation, his paternal grandparents had been granted temporary guardianship and were in the process of adopting the patient and his sister. His mother was given supervised visits on the weekends, during which time grandparents would notice acute decompensation in his behavior.

During his initial assessment in the clinic, he was noted to be intrusive, inappropriately hugging adults that he had just met, excessively talking, fidgeting, and having poor focus but with an otherwise euthymic mood. His grandmother noted he was not doing well in school, as he not only had difficulty with staying on task with work but also with rules and talking back to adults. He was described as "fearless," had nightly enuresis, and continued to suck his thumb. He denied feeling depressed, but the clinician did note excessive talking, poor concentration, hyperactivity, and oppositional traits (difficulty following rules, hitting too rough during play, and talking back to others). Upon review of his PTSD symptoms, findings were significant for bothersome dreams (which he would not remember the content of but would wake up wetting the bed), the avoidance of external

reminders of trauma (hence behavioral regression with his mother), inappropriate relationships with others (poor boundaries, difficult time attaching to caregivers), and irritable outbursts coupled with poor concentration.

How would you diagnose PTSD in Mr. Ashby, who is younger than 6 years old, based on the DSM-V?

1. **Criterion A: exposure to actual or threatened death, serious injury, or sexual violence: in the form of directly experiencing traumatic events is fulfilled**

2. **Presence of one or more of intrusion symptoms: frightening dreams without obvious content and repetitive play with a trauma aspect (seen as hitting too rough during play)**

3. **Regarding the presence of one or more avoidance symptoms or negative alterations in cognition of mood associated with trauma: Mr. Ashby did not exhibit negative alterations in cognition but did show avoidance of external reminders of trauma in that he would regress with his mother's presence**

4. **Two or more alterations in arousal associated with trauma are present: angry outbursts, poor concentration, sleep disturbance**

5. **In children younger than 6 years old, symptoms present for more than one month and disturbance causes distress or impairment in relationships or school behavior and is not due to substances or medical conditions.**

Summary

Traumatic events are common in people's lives. Most people who experience trauma will overcome it. However, some will experience short-term, non-disabling symptoms for a period up to months after the incident. A minority will develop mental health difficulties including, but not limited to PTSD. The risk factors for developing PTSD include female gender, low social support, a low *Intelligence Quotient* (IQ), a pre-existing psychiatric illness, and a family history of mood disorders, anxiety,

or substance abuse. Fortunately, a majority of PTSD cases can be treated using pharmacotherapy, CBT, or a combination of both depending on the presence of comorbid conditions which are common. Individuals exposed to repeated intentional trauma since childhood are likely to be more challenging to treat, and the treatment goal is to restore the victim's individuality and control. ◗◗

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Multiple-Choice Questions

1. **In which chapter is PTSD found when using the DSM-5?**

    A. Trauma and stressor-related disorders chapter

    B. Anxiety disorders chapter

    C. Disruptive, impulse-control, and conduct disorders chapter

    D. Neurocognitive disorders chapter

2. **What is the lifetime prevalence of PTSD in the United States?**

    A. 2.1%

    B. 6.8%

    C. 11.5%

    D. 33%

3. **Which medication is approved by the FDA for the treatment of PTSD?**

    A. Sertraline

    B. Risperidone

    C. Fluoxetine

    D. Venlafaxine

4. **What is the only first-line treatment of psychotherapy for the treatment of PTSD?**

    A. Psychodynamic psychotherapy

    B. Interpersonal therapy

    C. Trauma-focused *cognitive-behavioral therapy* (CBT)

    D. *Acceptance and commitment therapy* (ACT)

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Best Practices in CME

PTSD: Overview and DSM-5 Changes

By Lindsay N. French-Rosas, MD; Hazem Shahin, MD; and Asim A. Shah, MD

ID#: L003364

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to psychiatrists, family physicians, and therapists who require information on the prevalence of PTSD, the changes between the DSM-IV-TR and the DSM-5, the risk factors for the development of PTSD, and the pharmacological and non-pharmacological management of PTSD.

Key Point 1: Differences between the DSM-IV-TR and the DSM-5 criteria

There are significant differences in the diagnosis of PTSD with the new DSM-5. These include the new location of PTSD in the trauma and stressor-related disorders chapter, changes in key criteria clusters, and changes to the diagnosis of PTSD in children younger than 6 years old.

Key Point 2: Familiarity with Risk Factors in the Development of PTSD

Data suggest that many more people are exposed to trauma than those who actually go on to develop PTSD. Combat-related trauma, sexual trauma, and abuse or neglect are key triggers related to the development of PTSD in men, women, and children, respectively. Stress physiology plays an important role in the endocrine, neuroendocrine, and neuroimaging studies of patients with PTSD.

Key Point 3: Pharmacological Management of PTSD

Only sertraline and paroxetine are FDA approved for the management of PTSD, although many others show promising benefit. Specific symptoms clusters can be treated with certain medication classes, with novel medications being investigated for PTSD treatment.

Key Point 4: Non-pharmacological Management of PTSD

The IOM ranks trauma-focused CBT as the only first-line level of psychotherapy suitable for PTSD. The aim of CBT with the confrontation of traumatic memories and changing maladaptive patterns occurs through exposure therapy, CPT, EMDR, and stress inoculation training.

Notes

Substance Use Disorders:
An Overview, and Changes
in the DSM-5

Benjamin T. Li, MD; Edore Onigu-Otite; MD, Asim A. Shah, MD

KEY WORDS: Substance • Diagnosis • DSM-5 • Disorder

LEARNING OBJECTIVES: Upon completion of this lesson, clinicians will be able to recall the basic epidemiology and neurobiology of substance use disorders in adolescents and adults. Clinicians will be able to distinguish some of the similarities and differences in the diagnostic criteria for substance use disorders in the DSM-IV-TR and the DSM-5. Finally, providers will have an appreciation for how an accurate diagnosis can lead to appropriate psychopharmacologic and psychotherapeutic interventions.

LESSON ABSTRACT: Substance use disorder is a cause of significant morbidity and mortality with biological, psychological, and social influences. While substance use was previously defined as "abuse" or "dependence," the DSM-5 breaks away from this dichotomy and organizes substance use along a continuous spectrum of varying severities. The experience of substance craving has now been included as a criterion for substance use disorder, and recurrent legal issues secondary to substance use have been omitted. Other clinical diagnoses, such as caffeine withdrawal and cannabis withdrawal, are now formally recognized in the DSM-5. With these new diagnostic criteria, clinicians may have an improved ability to recognize and diagnose substance use disorders so that individuals may receive the most appropriate treatment.

COMPETENCY AREAS: This lesson discusses the changes in diagnostic criteria for substance use disorders in the DSM-5. Clinicians may neither be aware of some of these diagnostic changes nor know the rationale for these changes. Inaccurate diagnoses may ultimately lead to the underrecognition or overtreatment of substance use disorders, both of which may be detrimental to an individual's care. Upon the conclusion of this lesson, readers will have a greater understanding of the diagnostic changes that have occurred in the DSM-5, as well as basic treatment options for substance use disorders.

Overview and Prevalence of Substance Use Disorders

Substance use has led to significant morbidity and mortality in the *United States* (US). By understanding the epidemiology, neurobiology, and diagnosis of substance use disorders, clinicians can better appreciate the impact that treatment may have on this public health crisis.

Two major US studies, the *National Comorbidity Study Replication* (NCS-R) and the *National Epidemiological Survey on Alcohol and Related Conditions* (NESARC), both used the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria to estimate the prevalence rates of alcohol and substance use. The NCS-R, which sampled households between 2001 and 2003, estimated the lifetime prevalence of drug abuse to be 7.9% and lifetime prevalence of drug dependence to be 3.0%. The NESARC study, which sampled homes from 2001 to 2002 as well as from 2004 to 2005, predicted a similar lifetime prevalence of drug abuse at 7.7% and lifetime prevalence of drug dependence at 2.6%. However, estimates of lifetime prevalence of alcohol dependence were quite different, as NCS predicted 5.4% while NESARC predicted a significantly higher rate of 12.5%.[1]

Substance Use in Special Populations

Substance use disorders have also been studied in specific vulnerable populations. Based on the *National Survey on Drug Use and Health* (NSDUH), from 2012 to 2013, about 5.4% of pregnant women between ages 15 and 44 were illicit drug users.[2] The true amount of use may actually be higher than these estimates, due to the likelihood that some use is underreported.

Intravenous drug use also increases the risk of acquiring hepatitis C and the *human immunodeficiency virus* (HIV). In the US, it is estimated that 43% of intravenous drug users have chronic hepatitis C. Intravenous drug users are at an estimated 28 times higher risk of having HIV than the general population, and the risk of acquiring HIV with each injection may be as high as 2.8%.[3]

Within our nation's veterans, 70% of the homeless population report substance use problems.[4] Female veterans also have an estimated past-year rate of 3%–16% of substance use disorders.[5]

New findings from nationally representative samples of US youth reveal that the lifetime prevalence of alcohol use disorders is approximately 8% and illicit drug use disorders is 2% to 3%.[1, 6, 7] The median age at onset is 14 years for alcohol abuse with or without dependence, 14 years for drug abuse with dependence, and 15 years for drug abuse without dependence. The opportunity to use illicit drugs was reported by 81.4% of the older adolescents.[8] Epidemiological studies show a striking increase in the prevalence rates of substance use disorders between ages 12 and 18. In 2014, the rank order by age group for the annual prevalence of using any illicit drug was twelfth graders and college students (39%), 19- to 28-year olds (38%), tenth graders (30%), and eighth graders (15%).

Alcohol remains the substance most widely used by adolescents today. Past month alcohol use increases from 17% to 45% between eighth and twelfth grades, and illicit drug use prevalence increases steeply from 8% to 22%.[6] Among high school seniors, between 2005 and 2011 20.2% of high school seniors reported extreme binge drinking, with 10.5% reporting over 10 drinks and 5.6% reporting 15 or more extreme binge drinking episodes in the last 2 weeks.[9]

Following the recent legalization of marijuana in certain states, more youth are expected to use marijuana in the near future. An example is the effect on teens after California decriminalized marijuana use in 2010. From 2012 to 2013, compared to their peers in other states, Californian twelfth graders were 20% less likely to perceive regular marijuana use as a great health risk, 20% less likely to strongly disapprove of regular marijuana use, 25% more likely to have used marijuana in the past 30 days, and about 60% more likely to expect to be using marijuana 5 years in the future.[10] Of concern is also the use of synthetic cannabinoids. In 2011, the annual prevalence of synthetic cannabis was found to be 11.4%, making it the second most widely used class of illicit drug (after marijuana) among twelfth graders.[6]

With the introduction of e-cigarettes, epidemiological studies show that e-cigarettes now surpass tobacco cigarettes among teens, and users include youth who do not use traditional drugs of abuse.[11] Also, according to the NSDUH of 2010, about 11.4% of individuals aged

12 to 25 used prescription drugs non-medically within the past year. Recent studies show that 25% of those who began abusing prescription drugs at age 13 or younger met the clinical criteria for addiction sometime in their life and that use of prescribed opioids before the twelfth grade is independently associated with future opioid misuse among patients with little drug experience and who disapprove of illegal drug use. [12]

Adolescent substance use disorders are associated with high-risk behaviors. Every year in the US, approximately 5,000 young people under the age of 21 die as a result of underage drinking. This includes 1,900 deaths from motor vehicle crashes; 1,600 from homicides; 1,200 from alcohol-related poisoning, falls, burns, and drowning; and 300 from suicides.[13] Each year, large numbers of US high school seniors put themselves and others at great risk of harm by driving (or being the passenger of a driver) under the influence of marijuana, other illicit drugs, and alcohol.

The Neurobiological Model of Substance Use Disorders

Substance use disorders are influenced by a combination of biological, developmental, psychological, and social factors. Yet, it is estimated that only 15% to 20% of those who use substances will end up meeting criteria for dependence.[14] Perhaps specific genetic variations may be either protective or lead to increased vulnerability to developing addiction. For example, functional variants of the mu opiate receptor gene OPRM1 (opioid receptor mu 1) may have different risks for developing opiate addiction. The polymorphism of the CHRNA (ACh-Ralpha-subunit gene)[4] acetylcholine receptor may affect the development of nicotine dependence. Variations in genes encoding alcohol dehydrogenase may influence the risk of development of alcohol dependence.[15] **Genetic studies (including family, twin, and adoption studies) estimate that 30% to 70% of addiction is genetically influenced. It is likely that a number of different genes, as opposed to a single gene, cumulatively lead to this effect.[16]**

Different neurotransmitter systems may have a role in the development and maintenance of addiction, including but not limited to dopamine, glutamate, serotonin, and norepinephrine. However, one of the most popular theories is that substances of different classes ultimately lead to alterations within the *mesolimbic dopamine system* (MDS).

Within the MDS, dopaminergic neurons extend from the *ventral tegmental area* (VTA) of the midbrain to the *nucleus accumbens* (NAc) located in the striatum. A release of dopamine in the NAc is related to the increased salience attribution to cues that predict drug reward[17] and therefore reinforces the drug-seeking behavior. Some substances, such as cocaine and amphetamines, can directly increase dopamine through reuptake inhibition at the nerve terminal at NAc. Other substances may have a more indirect effect by involving pathways that eventually affect the presynaptic release of dopamine from the terminal at NAc (see *Figure 1*).[14] Such initial releases of dopamine are associated with the "initiation" or reinforcing process of addiction. However, *positron emission tomography* (PET) and *single-photon emission computed tomography* (SPECT) studies have suggested that while a more acute drug administration-induced increase of dopamine in the striatum is associated with a reward or "high" in alcohol, cocaine, stimulant, and heroin addiction, there may be an overall reduced striatal dopamine transmission with chronic use.[18] This reduction in dopamine transmission may parallel the cognitive shift from "liking" a substance into "wanting" or "needing" (i.e., developing an "addiction" to) it. Reduced striatal dopamine in these addicted subjects may include lower striatal dopamine receptor concentrations or a reduced dopamine response to a drug challenge.[19] Other studies suggest that long-term addiction is actually associated with a reduction in dopamine D2 receptor activation, and that lower dopamine transmission may be tied to a reduced response to treatment.[18]

Various neural pathways that have connections to the VTA and NAc may mediate the behaviors and impulses that drive addiction. These pathways may also be altered in the addiction process. While the amygdala-striatal system may influence the "impulsive" or automatic motivational and behavioral aspects of drug-seeking, the orbitofrontal and ventromedial prefrontal cortexes are structures that may control these impulses to seek drugs and allow the ability to weigh the short-term gains against the long-term consequences of an action.[17]

Figure 1:
Simplified Diagram of How Various Proposed Substances May Act Directly on Dopamine Release at the Nucleus Accumbens (NAc), or Have an Indirect Effect
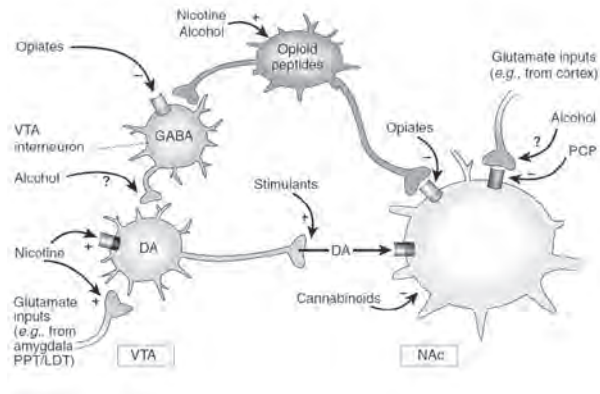
Stimulants such as cocaine and amphetamines lead to a direct increase of dopamine at the nerve terminal at the NAc. Other substances such as opiates may act indirectly by inhibiting the GABAergic interneuron within the VTA. This leads to the disinhibition of the dopaminergic neuron that extends to the NAc. Another example is alcohol leading to the release of endogenous opioid peptides such as beta-endorphins that then disinhibit the GABAergic interneuron.

Figure reprinted by permission from Macmillan Publishers Ltd. [Nature Neuroscience] (Nestler, EJ. Is there a Common Molecular Pathway for Addiction? *Nature Neuroscience*. 2005; 8(11):1445-1449). Copyright 2005.

Neurobiology in Adolescence

Adolescence is a period of rapid neurodevelopment involving complex biological, psychological, and social changes. Data from multiple imaging modalities continue to reveal the implications of brain changes on cognition, emotion, and behavior. During adolescence, synaptic pruning and myelination occur in various areas of the developing brain. Longitudinal MRI studies of subjects from ages 3 to 30 years demonstrate a general pattern of childhood peaks of gray matter followed by adolescent declines, functional and structural increases in connectivity and integrative processing, and a changing balance between limbic/subcortical and frontal lobe functions.[20, 21, 22] **The rapid brain development that occurs in adolescence is associated with heightened vulnerability to the effects of tobacco, alcohol, and illicit drugs on the brain.**[23, 24] While the developing brain

may be more resilient to neurotoxic effects, exposure to alcohol and drugs during this period of critical neuro-development may interrupt the normal course of brain maturation and key processes of brain development.[25] Neurocognitive deficits resulting from these alcohol- and drug-related neural insults have potentially harmful implications for subsequent academic, occupational, and social functioning extending into adulthood.[25, 26]

Changes in Diagnostic Criteria in the DSM-5

The DSM-IV-TR divides the diagnoses of substance use into either substance abuse or substance dependence categories. Under the DSM-IV-TR, a patient would often meet criteria for substance abuse if recurrent use has lead to social and interpersonal problems, substance-related legal problems, use in physically hazardous situations, and difficulty in fulfilling role obligations. At least one out of the three criteria had to be met within a 12 month period to obtain the diagnosis.[27]

Substance abuse tended to imply that there was impulsive substance use, and that, essentially, it could be controlled. On the other hand, substance dependence tended to imply a *loss of control over use*, similar to having a *compulsion*.

According to the DSM-IV-TR, one would often have a diagnosis of substance dependence if there were adequate signs of development of tolerance and withdrawal, difficulty in cutting down or controlling use, spending large amounts of time related to substance use, difficulty in fulfilling life roles due to use, and having continued use despite known psychological and physical consequences. At least three out of the seven criteria had to be present within a 12-month period to obtain the diagnosis.[27]

The most prominent change is the deletion of the abuse and dependence diagnoses in the DSM-5, which have been replaced by *use disorders*. Essentially, the 4 criteria for abuse and the 7 criteria for dependence are consolidated into a "pool" of 11 total criteria. The only exception is that withdrawal criteria are omitted from phencyclidine, other hallucinogen, and inhalant use disorders, as withdrawal has not been documented (or acknowledged in the DSM-5 as withdrawal syndromes) with the use of these respective substances. For all other

substances, meeting at least 2 out of the 11 criteria will lead to a diagnosis of a use disorder.[28]

Out of those 11 total criteria, 10 remain unchanged from the DSM-IV-TR. However, the criterion of recurrent legal consequences has been omitted for a use disorder despite many subjects having legal issues. This will reduce confusion in diagnosis due to variation in the legality of substance use on the national (e.g., recreational use of cannabis) and international levels. Another reason for the exclusion of legal criteria was based on a review of data that there is actually a low prevalence in adult samples. This criterion was also not very informative for distinguishing problematic users; it had low discrimination (how well the criterion differentiates between respondents with high and low severity of the condition). Moreover, patients did not report substance-related legal problems as a sole criterion, and never "lost" a substance use disorder diagnosis even if this criterion was omitted.[29] **In lieu of this criterion is the inclusion of** *cravings.* Cravings, defined in the DSM-5 as a "strong desire or urge to use," have been known to be a common characteristic of use disorders. The strength of cravings can influence drug intake, and neuroimaging suggests that cue-induced cravings can activate regions of the prefrontal cortex, amygdala, hippocampus, insula, and VTA.[30] Craving is included in the *International Statistical Classification of Diseases and Related Health Problems*, tenth revision (ICD-10), so this will keep diagnostic criteria consistent. Studies suggest that craving is a risk factor for relapse, which is a common part of the addiction process.[31] Cravings may have potential use as a biological treatment target.[29]

The severity of the use disorder is based on the total number of criteria met. Two to 3 criteria are sufficient for a "mild" specifier. Four to 5 criteria warrant a "moderate" specifier. Six or more criteria should be given a "severe" specifier. With DSM-IV-TR, severity of substance use diagnosis was typically not changed or "downgraded" over time. For example, one's diagnosis would not change from alcohol dependence to alcohol abuse, even if there were a reduction in consumption and consequences. In the DSM-5, the severity of a patient's substance use disorder can change over time.[28]

There are 10 categories of substances under the DSM-5: alcohol, caffeine, cannabis, hallucinogens (including PCP), inhalants, opioids, sedatives/ hypnotics/anxiolytics, stimulants (including cocaine), tobacco, and other. The *other* **category involves substances including but not limited to steroids, cathinones, and nitrates. When a substance use disorder is listed, one must list the name of the substance itself, not the class.** For example, one would diagnose "severe alprazolam use disorder" instead of "sedative, hypnotic, and anxiolytic disorder." If a patient meets the criteria for a use disorder with several different substances, each specific diagnosis should be listed. For example, one would list mild cannabis use disorder, moderate alcohol use disorder, and severe methamphetamine use disorder.[28]

One critique of the DSM-IV-TR classification was that normal physiological dependence was often mislabeled as a maladaptive drug dependence (or "addiction"). The DSM-5 clarifies that tolerance and withdrawal are not counted as criteria if these develop normally during course of treatment, if they are the only criteria met, and if there is no other sign of compulsive or drug-seeking behavior. For example, tolerance and withdrawal may be expected in those who are taking medication doses as prescribed, even in mild to moderate amounts. In the absence of any other cravings, compulsivity, or social dysfunction, these 2 criteria would not count. Otherwise, the patient may incorrectly receive a severity rating of mild substance use disorder. This could ultimately adversely impact his or her future treatment. For example, a patient whose dose of lorazepam for severe panic symptoms was increased from 0.5 mg daily to 1 mg daily over the past year under supervision of a provider, who never takes more than prescribed, and who has no compulsive drug-seeking behavior, runs out of the medication when his script is accidentally misplaced. He experiences benzodiazepine withdrawal symptoms and presents to the emergency department in a panic. In the context of this clinical example, there is insufficient justification to diagnose a lorazepam use disorder. Although signs of physiological tolerance and withdrawal are present, they are not present in the context of drug-seeking or compulsive behavior. However, if this same patient ran out of medication early because of taking twice the prescribed amount due to strong cravings, and thus went through withdrawals, he could meet the criteria for a use disorder. Feigning symptoms or seeing multiple simultaneous

providers to obtain medication can also raise red flags for a use disorder.

The elimination of the abuse and dependence categories can also reduce ambiguity about the criteria of tolerance and withdrawal. The abuse diagnosis tended to imply a milder and more impulsive pattern of substance use, whereas the dependence diagnosis connoted a more severe compulsive type pattern. The criteria of withdrawal and tolerance were only included in substance dependence in the DSM-IV-TR, thus suggesting that they only occur in a more severe, compulsive state. However, it is known that tolerance and withdrawal can still occur even in milder substance use disorders. Eliminating the word "abuse," which carries a negative connotation, also reduces stigma about substance use.

Several problems also limited the utility of DSM-IV-TR diagnoses in adolescents. Substantial data indicate that DSM-IV-TR substance abuse and substance dependence are not distinct categories in adolescents and are best conceptualized as a single entity.[32, 33] Using DSM-IV-TR criteria, abuse symptoms of legal problems and hazardous use, and dependence symptoms of tolerance, unsuccessful attempts to quit, and physical-psychological problems, showed relatively poor discrimination of problem severity in adolescents.[34, 35] A different problem demonstrated by the data was that the DSM-IV diagnostic criteria for substance abuse (one of 4 criteria) and dependence (3 of 7 criteria) created unequal diagnostic coverage among adolescents with comparable levels of substance problems.[36] **Many adolescents and adults in clinical and community samples also fell into the "diagnostic orphans" category with only one or 2 dependence symptoms, which did not qualify for a formal DSM-IV abuse or dependence diagnosis.[37, 38]** Yet, prospective studies show "diagnostic orphans" have levels of substance use and related problems over follow-ups that are comparable to those with a formal DSM-IV substance abuse diagnosis.[39, 40] On the other hand, given that experimenting with drugs is not unusual in adolescence, due to the single-item threshold requirement for the DSM-IV abuse criteria some adolescents with relatively low levels of substance use qualified for a substance abuse category, a group conceptualized as "diagnostic impostors."[41, 42, 43]

While these changes in criteria may help simplify and clarify the diagnostic process, some new clinical questions may arise due to these changes. Many recent studies for drugs to treat substance use often relied on "dependence" criteria under the DSM-IV. While it is assumed that anyone meeting the criteria for dependence (with at least 3 criteria) would technically meet the criteria for at least a mild use disorder, the reverse may not hold true. Thus, it may not be clear if a medication with efficacy for alcohol dependence under the DSM-IV-TR would also help similarly in those with alcohol use disorder under the DSM-5, as their symptoms may have met different criteria.

Other changes in substance use diagnoses include the addition of some newly recognized withdrawal states. **While a theoretical "caffeine use disorder" is not recognized, caffeine withdrawal, which is characterized by symptoms such as headaches, concentration difficulty, and fatigue, is now included in the DSM-5. Cannabis withdrawal was also not previously included in the DSM-IV but is now included in the DSM-5.** A "polysubstance dependence" correlate is not included; "polysubstance use disorder" is not a diagnosis, and each specific substance use disorder should be listed under the DSM-5.[28]

Specifiers related to description of remission have changed. There is only "early remission" and "sustained remission." Specifiers such as "early full remission," "early partial remission," "full sustained remission," and "sustained partial remission" no longer exist. Moreover, **for a remission specifier, one must not meet any criteria for substance use disorder (with the exception of cravings) for 3 months.** In the DSM-IV-TR, the minimum threshold was for one month. The 3-month period was included because data indicate better outcomes for those retained in treatment for at least 3 months.[29]

The specifier for "on agonist therapy" has changed to "on maintenance therapy." The use of the word agonist seems to imply that only agonists or partial agonists (such as buprenorphine, methadone, and nicotine replacement therapy) were included in the pharmacological treatment of substance use disorders. "Maintenance therapy" better reflects the breadth of pharmacologic options that may also include

treatments that have antagonist properties (such as *naltrexone* [Revia, Vivitrol]).

The DSM-IV-specific specifier of "with physiologic dependence" or "without physiologic dependence" has been removed, as it was rarely used.

Treatment of Substance Use Disorders: Therapy and Medications (FDA-approved and Off-label)

There are a variety of treatment options for substance use disorders for adults, including both medications and psychotherapy. For alcohol use disorders, the *Federal Drug Administration* (FDA) has approved the use of *disulfiram* (Antabuse), *naltrexone,* and *acamprosate* (Campral). The off-label use of medication includes *topiramate* (Topamax, Qudexy), which in some studies may actually be more efficacious than naltrexone.[44] Some medications have also been studied for specific populations with alcohol dependence, such as use of ondansetron in early onset alcoholism.[45] *Baclofen* (Kemstro, Gablofen) has been studied for the treatment of alcohol dependence in those with cirrhosis.[46]

FDA-approved treatments for opiate use disorders include *buprenorphine* (Buprenex and Butrans), methadone (Methadose, Diskets), and naltrexone. Naltrexone, a mu-opioid receptor antagonist, may block the action and therefore the reinforcing effect of opioids. It is available in the US in tablet and injection form. However, buprenorphine (a mu receptor partial agonist) and methadone (a full mu opiate receptor agonist) may have some advantages over naltrexone in that they may reduce or even eliminate cravings, a hallmark of addiction. Buprenorphine and methadone are synthetic opiates themselves; thus, they are used with a harm-reduction approach. Under those treatments, one will still likely maintain physiological dependence on medication; however, one can greatly improve one's quality of life through the reduction of compulsive behaviors that typically lead to legal issues, psychosocial dysfunction, and medical problems.

For treatment of nicotine use disorder, FDA-approved treatments consist of *nicotine replacement therapy* (NRT) which includes the nicotine patch, gum, lozenges, nasal sprays, and inhalers. **Bupropion is another option, which is an acetylcholine receptor antagonist.** *Varenicline* (Chantix), a partial acetycholine receptor agonist, can reduce cravings.

At this time, there are no FDA-approved treatments for cannabis, cocaine, or amphetamine dependence. Some treatments that have been studied for cannabis use disorder include N-acetylcysteine,[47] *gabapentin* (Neurontin, Gralise),[48] and *dronabinol* (Marinol).[49] However, there is lack of evidence to support their routine clinical use. A variety of dopamine agonists have been studied for the treatment of psychostimulant addiction, but there are no consistent positive results.

Psychotherapeutic options include *motivational interviewing* (MI), *relapse prevention* (RP), *cognitive behavioral therapy* (CBT), and *contingency management* (CM). Twelve-step groups including *Alcoholics Anonymous* (AA) and *Narcotics Anonymous* (NA) are also helpful, as they are widespread and can meet frequently. Studies suggest their efficacy and improved outcomes are associated not just with attendance, but more so with level of involvement.[50]

Substance abuse disorders in adolescence are a complex illness, and comprehensive treatment often involves multiple domains, including mental health, family, educational, legal, and other social services. Regarding medications, most FDA-approved medications are not approved in individuals aged 17 and under. Therefore, medication use is often off-label. Notably, there is high comorbidity with other psychiatric disorders, which influence the onset and severity of substance abuse disorders in adolescents. FDA-approved medications for such psychiatric comorbidities may treat mood, anxiety disorders, stress- and trauma-related disorders, and neurodevelopmental disorders such as *attention-deficit hyperactivity disorder* (ADHD), etc.

Nevertheless, currently, most adolescent treatments are highly psychosocially based. Psychosocial treatments shown to be effective in adolescent substance use also include CBT, MI, and CM. Treatments involving adolescent families include *multidimensional family therapy* (MDFT), *brief strategic family therapy* (BSFT), *functional family therapy* (FFT), *adolescent community reinforcement approach* (A-CRA), and *assertive continuing care* (ACC). ACC is a home-based

continuing-care approach to preventing relapse, with weekly home visits taking place over a 12- to 14-week period after an adolescent is discharged from residential treatment.[51]

Although many adolescents use and abuse illicit drugs, only a few of those who could benefit from substance abuse treatment ever receive these services. Utilization of these services by adolescents has remained low and relatively stable over the past 22 years. Adolescents reporting a greater frequency of lifetime use of marijuana or cocaine were more likely to receive substance abuse treatment. Substance abuse treatment utilization was more likely in those who received other mental health services.[52] In some studies, random drug testing was associated with moderately lower marijuana use in general student populations. However, there was evidence to suggest drug testing in certain student subpopulations (athletes or participants in nonathletic extracurricular activities) was associated with the increased use of illicit drugs other than marijuana.[53] Other studies have found no association between student drug testing and illicit drug use.[54]

Clinical Cases:

Vignette 1

A 35-year-old male initially presented to an outpatient psychiatric appointment with elevated vital signs of 150/90 when he is usually normotensive. He frequently yawned during the visit and complained of nausea and diarrhea. He had been taking his other psychiatric medications, including *venlafaxine* (Effexor) and *trazodone* (Oleptro), regularly for the past 5–6 months.

The psychiatrist obtained the patient's history. After having sustained a femur fracture via a motor-vehicle accident about a year ago, he had been prescribed morphine 30 mg daily for 21 days. After the fracture was healed, he continued to obtain opiate medication even though he no longer was in pain. He noticed he felt "energetic and alive" when taking the opiates. To sustain this, he would feign being in pain to obtain more opiates from his provider, and he began to take more than prescribed. Within 3 months, he was seeing 3 different doctors and taking

30 tabs a day on average. Due to his use, he consumed all his savings to buy pain pills and quit work due to feeling "slowed down." He went to jail once after stealing to support his substance use. He spent the majority of his day trying to seek new providers who could prescribe the medication. After about 7 months, he believed it was too difficult to sustain his pattern of use and thus went to residential treatment on two separate occasions, for 30 days each. Despite completing both programs, he relapsed shortly after discharge.

Within the next week, the patient was started on *buprenorphine* (Buprenex, Butrans). He was able to stop using opiates and was stabilized on a dose of 8 mg daily. At this point in time, he has been on buprenorphine for 2 months without use of any other opiates during that entire time frame. What would his most current diagnosis be for both the DSM IV-TR and DSM-5?

Answer:

DSM-5: Severe morphine use disorder, on maintenance therapy. DSM-IV-TR: Opiate dependence, with physiological dependence, in early full remission, on agonist therapy

The patient under the DSM-IV-TR would meet criteria for opiate dependence because he meets at least 3 criteria for dependence. He also would be in early, sustained remission, as he has not met any abuse or dependence criteria for at least one month but less than 12 months. He would still receive an "on agonist" specifier since he is receiving buprenorphine therapy.

Under the DSM-5, he has a total of at least 6 criteria, thus meeting criteria for a substance use disorder of severe intensity. Remember that legal issues should not be included in the criteria. The specific substance of use (morphine) is noted in the diagnosis, instead of the class of substance. He would technically not be in early remission per DSM-5 guidelines, as the patient must be in remission for at least 3 months to have a remission specifier. Note that even though there are signs of physiological dependence, this is no longer a specifier in the DSM-5. In addition, the specifier of "on agonist therapy" has now been updated to "on maintenance therapy."

Vignette 2

A 15-year-old male who recently relocated from another state was seen for a routine well-child visit by his pediatrician, during which he screened positive for depression and was referred to an outpatient mental health clinic. In his initial interview, the patient reported he was unhappy with his life, having struggled for years with attention problems and bullying in school. He had never repeated a grade and had no disciplinary problems in school. He had no history of legal problems. Three months prior, he had been admitted to inpatient psychiatric hospitals for suicidal ideation. He had passive suicidal thoughts, a history of *non-suicidal self-injury* (NSSI), but had no suicide attempts. He lived with his mother and step-brother. His mother revealed that his biological father had a history of alcohol use and had died of a liver problem in a foreign country. The patient met criteria for both a major depressive disorder, single episode, severe, without psychotic features, and an anxiety disorder, not elsewhere classified, with the possibility of attention deficit disorder. He was started on *escitalopram* (Lexapro) and *aripiprazole* (Abilify). He tolerated escitalopram poorly, but was able to tolerate a switch to *sertraline* (Zoloft).

In follow-up appointments, the patient revealed he had taken his first drink of alcohol at age 13 and had a pattern of binge drinking. He did not consider himself an "alcoholic" because he only drank intermittently, sometimes going weeks without drinking. However, his abstinence from drinking was solely based on a lack of availability of alcohol. He still experienced cravings to drink. The patient revealed that he first got depressed after a traumatic experience after which he began drinking alcohol. In his words, *"I was anxious; that was why I drank."* He reportedly drank as much alcohol as he could find, and admitted to getting intoxicated on a daily basis. Following his inpatient hospitalization, he was stepped down to an intensive outpatient program that had a "zero tolerance" for substance use. He reported he was unceremoniously discharged after he revealed to staff that he had an alcoholic drink with his girlfriend. Following that experience, he had become cautious about revealing any substance use to his mental health providers. The patient was reassured that his treatment needs would be met. Given his symptoms of emotional distress associated with NSSI, he was referred to an outpatient clinic where he received dialectic behavior therapy to facilitate his coping skills, and he attended group therapy with male adolescents who had similar alcohol and drug use problems.

Routine monitoring labs were ordered, and the results revealed that the patient's liver transaminases had tripled, with an ALT to AST ratio of 2:1. The patient revealed that he had continued to binge drink, although less frequently than in the past. He was given a diagnosis of alcoholic hepatitis, and he was referred to the pediatric gastroenterologist. With this medical complication, he became motivated to abstain totally from alcohol use. Within 3 months, repeat labs showed that his liver transaminases had returned to baseline. The patient changed schools and still complains of difficulty with attention, but currently experiences less stress and has increased his social activity. He continues to engage in high-risk behaviors with his girlfriend. He continues to attend his medication management appointments and individual therapy appointments regularly. Random urine drug tests have been negative so far and seemed to serve as a deterrent for other illicit drug use.

Discussion:

Under the DSM-IV-TR, the patient met criteria for alcohol abuse, but perhaps would never have met criteria for alcohol dependence despite his end-organ damage directly associated with his destructive pattern of alcohol use and his high risk behaviors. Under the DSM-5, he meets criteria for an alcohol use disorder, which is likely to wax and wane over time, i.e., shift in severity from mild to severe over the course of his lifetime, given his genetic predisposition. The DSM-5 provides a more user-friendly approach to the diagnosis and corresponding treatment of substance use disorders in adolescents and for their providers.

Summary

Substance use disorders affect many people worldwide, including children and adolescents. Health providers may best be able to accurately diagnose problems related to substance use through thorough history-taking and application of DSM-5 criteria for substance use disorders. While the DSM-IV-TR criteria may be familiar, they may not reflect the most updated and research-based criteria found in DSM-5. The most notable difference between DSM-IV-TR and DSM-5 is the elimination of the 'abuse' and 'dependence' categories, and the consolidation of 11 total criteria under a sole 'substance use disorder' category. Some specifiers have also been updated, and clinical entities such as caffeine and cannabis withdrawal are now formally recognized under DSM-5. After a correct diagnosis is made, the treatment of biological, psychological, and social factors should be considered. 〉〉

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Multiple-Choice Questions

5. **Which of the following changes in diagnostic criteria for substance use disorders have been made when comparing the DSM-IV-TR to the DSM-5?**

    A. Addition of cravings as a criterion in the DSM-5

    B. Addition of recurrent legal issues in the DSM-5

    C. Removal of tolerance in the DSM-5

    D. Both A and C

6. **All of the following are recognized under the DSM-5,** *except***:**

    A. cannabis withdrawal.

    B. nicotine use disorder.

    C. alcohol use disorder, early remission.

    D. caffeine use disorder.

7. **All of the following medications are approved by the FDA to treat substance use disorders,** *except***:**

    A. buprenorphine.

    B. naltrexone.

    C. bupropion.

    D. topiramate.

8. **What is the most widely used substance by adolescents?**

    A. Cocaine

    B. Marijuana

    C. Alcohol

    D. Nicotine

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Best Practices in CME

Substance Use Disorders:
An Overview, and Changes in the DSM-5

By Benjamin T. Li, MD; Edore Onigu-Otite; MD, and Asim A. Shah, MD

ID#: L003365

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Substance use disorders are a significant cause of morbidity and mortality worldwide, and their treatment relies on accurate recognition and diagnosis. The DSM-5, while using many of the same criteria from the DSM-IV-TR "abuse" and "dependence" diagnoses, reconceptualizes substance use disorders as illnesses with varying severity.

Key Point 1: Notable Differences in Classification

DSM-5 uses the same combined 11 criteria that DSM-IV-TR uses for substance abuse and substance dependence, with the exception that recurrent legal issues has been removed as a criterion, and has been replaced by the experience of substance cravings.

Key Point 2: Newly Recognized Withdrawal Syndromes

Clinical diagnoses such as caffeine withdrawal and cannabis withdrawal are now formally recognized in DSM-5.

Key Point 3: Neurobiology of Substance Use Disorders

Several brain structures may be involved in the development of addiction, including the ventral tegmental area and nucleus accumbens. Children and adolescents may be in a state of rapid brain development, and they may be more vulnerable to the effects of substances.

Key Point 4: Substance Use Disorders Treatment Options

There is a limited range of options for pharmacological treatment of substance use disorders in adolescents and adults; however, there is a variety of psychotherapeutic options that may have some utility such as: such as cognitive-behavioral therapy, motivational interviewing, and contingency management.

Notes

Somatic Symptoms and Related Disorders: Overview, Updates, and Changes in the DSM-5

Jin Y. Han, MD; Lindsay N. French-Rosas, MD; and Asim A. Shah, MD

KEY WORDS: Somatic • Somatoform • DSM-IV-TR • DSM-5

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) describe the new DSM-5 diagnostic criteria for Somatic Symptom and Related Disorders; (2) compare changes from the DSM-IV-TR; and (3) discuss the epidemiology, pathogenesis, and different treatment modalities.

LESSON ABSTRACT: Studies find that patients whose focus primarily involves physical complaints experience less improvement, exhibit more disability, and utilize medical services more frequently. By exploring the epidemiology, pathogenesis, and changes between the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision* (DSM-IV-TR) Somatoform Disorders and the DSM-5 Somatic Symptom and Related Disorders, including treatment options, clinicians will feel more equipped to deal with this oftentimes challenging patient population.

COMPETENCY AREAS: This lesson addresses the gap in knowledge of the new DSM-5 diagnostic criteria for Somatic Symptom and Related Disorders, including an overview of the epidemiology, pathogenesis, and treatment modalities.

Introduction

It is not uncommon for someone to present at their outpatient visits or emergency rooms with a constellation of physical symptoms. A complicated physical picture frequently leads to an extensive medical workup and numerous examinations. It is also not uncommon for medical causes to go unidentified despite a thorough search and these patients then go on to seek out other services. This often creates tension or frustration for both patient and provider. Researchers have found that patients whose focus primarily involves physical complaints experience less improvement, exhibit more disability, and utilize medical services more frequently. By exploring the epidemiology, pathogenesis, and changes between the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision* (DSM-IV-TR) and the fifth edition of the same manual (DSM-5) as well as the treatment options, clinicians will feel more equipped to deal with this oftentimes challenging patient population.

Patients with somatic symptoms classically experience less remission and greater overall impairment. **A 5-year follow-up study identified a group of patients with unexplained physical symptoms who experience less clinical improvement and have significant functional impairment as well as higher medical utilization rates.[1] Patients with somatization had approximately twice the outpatient and inpatient medical care utilization and twice the annual medical care costs compared to non-somatizing patients.** Adjusting the findings for the presence of psychiatric and medical comorbidity had relatively little effect on this association.[2] Patients with somatization had substantially greater functional disability compared to non-somatizing patients and its severity was equal to or greater than that associated with many major and chronic medical disorders. Adjusting the results for psychiatric and medical comorbidity had little effect on these findings.[3] Several studies have suggested that up to 50% of primary care patients present with medically unexplained symptoms,[4] which are associated with impaired quality of life, increased health care use, and diminished patient and provider satisfaction.[5]

To identify and best treat this population, one must take a thorough history. A good biopsychosocial history, including a review of previous medical records and further collateral information from the family, may suggest significant impairment in daily functioning, including emotional suffering, worrying, and searching for further answers regarding their physical symptoms and health status. Further screening may also suggest comorbid depression, anxiety, underlying characterological traits (particularly Histrionic, Borderline, and Antisocial traits), and poor coping skills including substance misuse.[6-10]

There are several noteworthy changes to this category since the DSM-5 uses the term *Somatic Symptom and Related Disorders* rather than the previous DSM-IV-TR term *Somatoform Disorders*, and it includes a new set of diagnoses, such as Somatic Symptom Disorder; Illness Anxiety Disorder; Conversion Disorder or Functional Neurological Symptom Disorder; Factitious Disorder; Psychological Factors Affecting Other Medical Conditions; Other Specified Somatic Symptom and Related Disorder; and Unspecified Somatic Symptom and Related Disorder.[11] In the DSM-IV-TR, the key emphasis was that symptoms were not explained by a general medical condition. Conversely, in the DSM-5, the clinical focus relies on the level of impairment of daily functioning and distress due to physical symptoms or health-related concerns, regardless of a medical explanation. One exception to this, however, is Conversion Disorder and Pseudocyesis (included under "Other Specified Somatic Symptom and Related Disorder" by DSM-5 Classification) where a workup can rule out medical conditions.[12]

Epidemiology

Most of the statistical data come from the DSM-IV-TR era. At any given time, approximately 80% of the general population reports somatic symptoms in the last 7 days, and roughly every fifth person has developed at least one severe somatization symptom.[12, 13] According to a study calculating the economic cost of brain disorders in Europe, an estimated 20.4 million subjects are affected by somatoform disorders, which is quickly becoming one of the top 5 psychiatric conditions.[14] The median prevalence of somatization was approximately 16.6% in primary care settings.[15] Another systematic review of several European studies found the median 12-month prevalence rate for somatoform disorders to be close to 5%–6%, occurring more frequently in women, older patients, and those with lower socioeconomic and educational statuses.[11, 16, 17] Approximately 20% of first-degree

female relatives of patients with somatization disorder also met criteria for the same condition, but male relatives were more likely to have a comorbid substance use disorder or antisocial traits.[18] Minority populations have higher risks as well, likely due to higher rates of traumatic events.[19]

The 1-year prevalence of Hypochondriasis in the general population is estimated to be 1%–10%, but the range gets narrowed to 3%–8% in primary care outpatient settings. It is important to keep in mind that approximately 25% of these patients would meet criteria for the new Illness Anxiety Disorder diagnosis, and the other 75% would instead meet criteria for the new Somatic Symptom Disorder diagnosis based on DSM-5 Classification. Illness Anxiety Disorder tends to begin in early adulthood and has a chronic fluctuating pattern, but its prevalence seems to be similar in males and females. Approximately two-thirds of patients with Illness Anxiety Disorder have at least one major comorbid psychiatric condition.[11]

Conversion Disorder is 2–3 times more common in females and comprises up to 3% of outpatient referrals to mental health clinics. Similar recurrent symptoms have been identified in approximately 1% to 14% of the medical and surgical inpatient population.[11, 17] Some authors suggested a prevalence estimate of 1% to 4% in the medical population.[38] Diagnosis could be a challenge, as 5% to 15% of these patients are estimated to have neurological conditions.[47]

Pain Disorder (or Somatic Symptom Disorder with predominant pain per DSM-5 classification) may occur at any age. Although the prevalence has not been quantified, it is relatively common in certain medical settings, such as primary care or pain clinics. Psychological Factors Affecting Other Medical Conditions can also occur at any age but its prevalence is unclear.[11, 17]

Factitious Disorder is estimated to occur in approximately 1% of hospitalized patients, but more accurate data are difficult to obtain due to the role of deception; however, patients are more likely to be females in early adulthood.[11, 17, 39, 48]

Pathogenesis

The development of Somatic Symptom and Related Disorders is thought to occur due to a constellation of early life experiences, such as trauma, the impact of sociodemographic factors, and biological vulnerability. It is hypothesized that hormonal differences could explain the prevalence in females, but men's risk becomes higher if traumatic events are part of the equation. Comorbidity with other mental illnesses such as Posttraumatic Stress Posttraumatic Disorder, Depressive Disorders, Substance Use Disorders, and Personality Disorders suggest a strong correlation of trauma as an important etiological factor. Patients may report a history of a significant loss of loved ones or abandonment and poor attachment to caretakers. Psychodynamic theories suggest unresolved unconscious emotional conflicts, negative affectivity mixed with maladaptive coping mechanisms, learning processes such as getting attention from being in the sick role, an inability to express emotional states, defense against psychosis or need for identity, and internalization or displacement of anger. Individuals' vulnerability relies on the concept that sensitivity to bodily signals seems more elevated in certain individuals with a tendency to over interpret such physical sensations. Adoption studies indicated the role of genetic and environmental factors in the development of Personality Disorders, Substance Use Disorders, and Somatic Symptom and Related Disorders. Cultural background could be influential as well since the stigma of mental illnesses is more noticeable in certain populations, even though medically unexplained somatic symptomatology is seen worldwide.[17, 19, 40-44, 50]

DSM-IV-TR and Somatoform Disorders

As stated above, the DSM-IV-TR emphasizes medically unexplained symptomatology, but the DSM-5 focuses on impaired daily functioning and distress due to physical symptoms or health-related concerns.

1. **Somatization Disorder includes a constellation of unexplained physical symptoms (including at least 4 pain sites or functions, 2 gastrointestinal symptoms, one sexual, and one pseudo-neurological symptom), which began before the age of 30, causing significant impairment in functioning.**

2. **Undifferentiated Somatoform Disorder is characterized by at least one unexplained physical**

symptom lasting 6 months or more causing significant impairment in daily functioning.

3. **Conversion Disorder includes at least one medically unexplained symptom or deficit affecting voluntary motor or sensory function that suggests a neurological or other general medical condition, preceded by psychosocial stressors, and leading to significant impairment in functioning. It is important to note that up to one-third of individuals with conversion symptoms have a current or prior neurological condition, but further examination does not fully explain the new chief complaint.**

4. **Pain Disorder is characterized by at least one pain site as the predominant focus of clinical attention causing significant distress, where psychological factors could be identified with or without an identified general medical condition.**

5. **Hypochondriasis is diagnosed when there is preoccupation with fear of having a serious medical disease based on the person's misinterpretation of bodily symptoms, which persists despite appropriate medical evaluation and reassurance, leading to significant distress or impairment in functioning lasting 6 months or more.**

6. **Body Dysmorphic Disorder includes an excessive preoccupation with defects (imaginary or slight flaws) in physical appearance causing significant distress.**

7. **Somatoform Disorder Not Otherwise Specified is coded when somatoform symptoms do not meet criteria for any of the specific Somatoform Disorders mentioned above. Pseudocyesis (which includes a false belief of being pregnant associated with objective findings like abdominal enlargement, amenorrhea, a subjective sensation of fetal movement, nausea, breast engorgement, and secretions) is included under this category.**

DSM-5 and Somatic Symptom and Related Disorders

In the DSM-5, the diagnoses of Somatization Disorder, Hypochondriasis, Pain Disorder, Body Dysmorphic Disorder, and Undifferentiated Somatoform Disorder have been removed or reorganized under different categories, terms, or diagnoses. Factitious Disorder was included in this category. Conversion Disorder is the only term or diagnosis grandfathered into the new DSM-5.

Somatic Symptom Disorder (SSD):

SSD is characterized by at least one physical symptom that disrupts the quality of daily life, accompanied by excessive thoughts, feelings, or behaviors regarding its severity, lasting for at least 6 months. A lack of medical etiology is not enough to make this diagnosis; in fact, it can be associated with an underlying medical condition, but the key point is that the level of distress is significant. **Many patients with SSD are quite worried that they might actually have a serious medical illness despite reassurance; therefore, it is estimated that approximately 75% of patients meeting DSM-IV-TR criteria for Hypochondriasis would be included under this new diagnosis.** Patients seem to misinterpret some physical symptoms or bodily sensations, leading them to seek further medical care, but once again the focus is not on number of symptoms but the level of distress surrounding the symptoms. Excessive and repetitive medical tests or procedures (e.g., radiation exposure, invasive procedures, surgeries) are commonly seen, which would also lead to more complications for the patients. Patients also show some avoidant behaviors (e.g., avoiding physical activities) due to fear that the condition might get worse.

SSD can be divided based on severity into mild (only one symptom), moderate, and severe (2 or more symptoms). As mentioned above, Pain Disorder is coded as Somatic Symptom Disorder with predominant pain. Previous patients diagnosed with Somatization Disorder in the DSM-IV-TR will likely meet criteria for SSD in the DSM-5 with the "severe" specifier included, but they must also have the excessive thoughts, feelings, and behaviors, as mentioned above.

Illness Anxiety Disorder (IAD):

IAD is diagnosed when there is excessive preoccupation with having a serious illness but physical symptoms are minimal or not present at all, lasting for at least 6 months. The patients' level of anxiety is high, associated with maladaptive "care-seeking" or "care-avoidant" behaviors, which would be coded as specifiers. **The key feature here is that physical symptoms are not required for diagnostic purposes.**

These patients spend a significant amount of time researching their possible serious condition, either on the internet, in books, or by talking to family, friends, or health professionals. Patients with IAD, care-seeking type get repetitive medical reassurances that do not last long or are not satisfactory. As stated above, it is estimated that 25% of patients diagnosed with Hypochondriasis per the DSM-IV-TR would meet criteria for this new diagnosis.

Conversion Disorder (CD) or Functional Neurological Symptom Disorder:

CD includes at least one symptom of altered voluntary motor or sensory function causing significant impairment in functioning, but clinical findings (e.g., neurological exam) are not compatible with the possible neurological or medical condition being considered. **The key point relies on the importance of physical examination or medical workup results rather than the presence of psychological factors in the clinical picture.**

CD is often associated with dissociative symptoms like depersonalization, derealization, or dissociative amnesia, and further specifiers could be used to describe the symptom type, such as "with weakness or paralysis; with abnormal movement; with swallowing symptoms; with speech symptom; with attacks or seizures; with anesthesia or sensory loss; with special sensory symptom; with mixed symptoms." It is important to avoid labeling it as "psychogenic or functional" too early, until clear medical evidence suggests incompatibility with the suspected neurological condition.

Psychological Factors Affecting Other Medical Conditions:

This DSM-5 diagnosis has been formerly classified under the chapter of "Other Conditions That May Be a Focus of Clinical Attention" in the DSM-IV-TR. Here the medical condition or symptom exists, but psychological or behavioral factors influence the course or outcome of the illness or interfere with treatment adherence. It could be specified as mild, moderate, severe, or extreme based on its severity.

Factitious Disorder (FD):

In the DSM-IV-TR, Factitious Disorder was mentioned in a separate chapter, but this diagnosis is now included in the DSM-5 "Somatic Symptom and Related Disorders" section. The diagnostic criteria include the falsification of physical or psychological signs or symptoms or induction of injury or disease associated with identified deception, but there are no obvious external rewards (e.g., money, placement). The condition could be "imposed to self" or "imposed on another (formerly called *FD by Proxy*)." The ultimate goal of the patients seems to be related to the emotional benefits of taking the sick role. Previous medical conditions may be present, but the actions of the patients can make them look worse.

Other Specified Somatic Symptom and Related Disorder:

This diagnostic is used when full criteria are not met for any of the Somatic Symptom and Related Disorders, either because the minimum 6 months duration or another criterion is not met (e.g., Brief SSD and Brief IAD when less than 6 months in duration; IAD without excessive health-related behaviors). Pseudocyesis is included under this DSM-5 category rather than the DSM-IV-TR Somatoform Disorder Not Otherwise Specified.

Unspecified Somatic Symptom and Related Disorder:

This term should be used when there is insufficient information to make more specified Somatic Symptom and Related diagnoses.

Clinical Cases:

Case 1

A 65-year-old Asian female presented to the clinic after referral from her neurologist, with a history of undiagnosed medical conditions for many years. She and her husband immigrated to the United

States from China 40 years ago to complete their education here. She went on to have a successful career in finance, what she would describe as a good marriage, and 2 healthy sons, with whom she is still very close. She was diagnosed with breast cancer and underwent lumpectomy when she was 50 years old, leading to premature retirement. Since that time, she has spent her days at home with her husband. She has gone on to experience significant medical conditions, including chronic pain, deconditioning, constipation, heaviness in her legs and head, a "pulling" sensation in her stomach and head, shooting pains in her entire body, weight loss, global weakness, dry mouth, burning tongue, palpitations, chills, shortness of breath, and malaise. Additionally, she was unable to stand without balance difficulty with her eyes closed and walked with a slow gait. She had been seen by numerous specialists, including an internist, neurologist, neurosurgeon, and oncologist. She underwent numerous medical evaluations, procedures, and imaging studies, all of which were negative other than breast cancer and osteopenia. She was eventually referred to psychiatry, as she was told "a chemical imbalance in your head" was causing her medical distress. On evaluation, she reported a history of depression and anxiety for which she had been on clonazepam 2 mg at bedtime for 30 years and sertraline 50 mg daily for the past several months. She felt there was benefit with clonazepam in terms of sleep, but did not notice any improvement with sertraline, as she did admit to low mood, poor energy, decreased appetite, and hopelessness. She reported passive suicidal ideation, stating she worried she would be "tortured" to death, but identified family and religion as protective factors against suicide. Mental status exam was significant for a frail, elderly-appearing woman, slumped over in the chair, gait slow with staggering steps, affective anxiety with frequent questioning, and incongruence with her stated mood as "calm." Further questioning revealed that she was feeling overwhelmed and isolated, as her medical conditions make it impossible for her to engage in life as she once did.

What DSM-5 criteria would you use to point to a diagnosis of Somatic Symptom Disorder?

Answers:

Patient exhibits criterion A, as she has one or more somatic symptoms that are distressing or result in significant disruption of her daily life.

Although she does have medical conditions with founded etiology, such as her breast cancer, she still exhibits elevated levels of distress beyond what would be expected for her medical condition.

Criterion B is met, as she has excessive thoughts, feelings, and behaviors related to the somatic symptoms of associated health concerns.

Patient has devoted an exceptional amount of time to her symptoms, to the point where she is no longer able to work and now exhibits avoidant behaviors (such as rarely walking) out of fear her illnesses would progress.

Specifiers of persistent (as she has had these for more than 6 months), severe (as she has 2 or more symptoms specified in Criterion B and 3 are multiple somatic complaints), and with behavioral features (repeated seeking of medical help) apply.

Case 2

A 55-year-old Hispanic woman with a history of self-reported depression and anxiety who presented on her own for a second opinion. She saw a psychiatrist one year prior to the current visit, but felt that the visit was focused too strongly on medication management of depression and anxiety and she wanted someone to "take the whole picture into account." By this, she explained she wanted treatment by an expert who could understand how her medical conditions impacted her mental health. Her fatigue and variable sleep were worsening to the point where she felt she needed to re-establish care with another psychiatrist.

Her history revealed that she had been doing well, working in a contract position at laboratories across town, until 5 years ago when she lost her job, became homeless, and concurrently experienced a myriad

of health problems. She had allergies to dust, chest pain, heaviness in her legs, shortness of breath, vein pain, cramping pain in her legs, proximal muscle weakness, difficulty with extension and flexion of her lower extremities, anemia, dizziness, fear about having Parkinson's disease due to a swaying sensation while walking, muscle tension in her face and jaws, tinnitus, and the growth of thick dark hair. In addition, she was convinced she had congestive heart failure due to fatigue and a pituitary tumor due to poor concentration, despite the cardiac workup and MRI both being negative. Her other medical problems included being in menopause for 5 years without hormone replacement therapy, obstructive sleep apnea while not using a CPAP, and hypothyroidism with supplementation. She dominated exams with multiple providers. Specialists had described her as "perseverative" on her somatic symptoms, "difficult to redirect," and "refutes attempts to redirect conversations." She had refused many medications and routine exams, including well woman exams, mammograms, and routine blood work, insisting this all made her feel more overwhelmed. The psychiatric examination was significant for somatic perseveration, anxious affect, but a well-appearing overweight woman. Similar to other treatment providers, she refused all psychotropic medications and insisted on being seen by a psychiatrist who would provide therapy only. Once this was arranged, she stopped visits after 3 sessions with no clear reason.

What treatment modalities would you consider to best manage this patient?

Answers:

Pharmacological approach: *Antidepressants have been shown to be moderately effective overall, although no clear benefit exists with using one class over another.*

Pharmacological approach for comorbid presentation: *Consider the use of serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), as these classes of antidepressants are helpful with comorbid pain and depression. For comorbid depression and anxiety, consider selective serotonin reuptake inhibitors (SSRI) or SNRIs.*

Suicide risk assessment: *Be mindful that the suicide risk level is higher in patients with comorbidities and one should assess for safety.*

Psychotherapeutic approach: *Cognitive behavioral therapy (CBT) is considered the most effective evidence-based approach, although often patients are resistant to therapy. To form a cohesive union with the patient, avoid confrontation, provide reassurance and validation, and work with the patient to establish realistic goals.*

Psychoeducational approach: *Collaborate with patient's primary care provider (PCP), as the psychiatrist is typically a consultant. Recommend that the PCP see the patient regularly, establish good rapport, and validate her level of distress over somatic concerns. It may be helpful to also educate the family and the patient on coping strategies.*

Treatment

There are no FDA-approved medications for any of the Somatic and Symptom and Related Disorders. A systematic review looking into the pharmacological interventions for Somatoform Disorders included 26 randomized control trials comparing the efficacy of different antidepressants, a combination of antidepressants and antipsychotics, antipsychotics alone, and natural products. The evidence was low in quality compared to a placebo, and it was also noticeable that adverse effects were more problematic for these patients who were already dealing with high sensitivity to their own bodily sensations. Nonetheless, antidepressants seem to be moderately effective overall for unexplained physical symptoms, anxiety, and depression in Somatic Symptom and Related Disorders.[54, 62-63, 67]

Some psychotherapeutic modalities have been suggested, but CBT is considered the most effective evidence-based approach.[26, 47] Educational interventions involving the patient and his/her family can help them learn new coping strategies to deal with the symptoms, but the overall treatment process could be lengthy and complex, as many of these patients are quite defensive regarding psychiatric explanations or psychotherapeutic interventions. Most patients will be seen in non-psychiatric settings; thus, psychiatrists primarily play the role of consultants. The primary clinician should focus

on establishing good rapport with the patient, empathizing and validating the patient's distress due to physical symptoms. A confrontational approach is discouraged, since debating about the medical versus psychiatric etiologies will not lead to better outcomes. The clinician should offer professional advice in a nonjudgmental way, focusing on goals to improve the patient's level of functioning; both the clinician and the patient should design a realistic treatment plan in which further medical evaluations or procedures will be done judiciously, communicating each result objectively, scheduling regular visits, coordinating care with other clinicians or specialists but avoiding unnecessary referrals, and prescribing medications to ameliorate symptoms if needed. The reassurance that the clinician will continue working with the patient (regardless of the test results) to accomplish such goals will enhance rapport and mutual trust.[49, 51, 53, 55-57, 64-66]

If there are comorbidities such as depression and anxiety, clinicians should explain the benefits of treating them appropriately with medications like SSRIs or SNRIs and psychotherapy. SNRIs and TCAs have been helpful for patients with comorbid physical pain and depression.[60-61, 68, 69] In the context of comorbidity, completing a safety assessment is important since the suicide risk level is higher in patients with comorbidities.[17] Substance use disorders should be treated as well; therefore, clinicians should avoid potentially addictive medications. Other psychotherapies can be helpful, including but not limited to family therapy, supportive therapy, stress management, and psychodynamic psychotherapy as well as relaxation techniques or exercises.

For patients with CD, the main intervention relies on psychoeducation, leaving CBT and/or physical therapy as adjunct interventions, particularly if there is a motor symptom or the education itself was not effective. Other interventions like pharmacotherapy or psychodynamic psychotherapy have been attempted in refractory cases.[58-59,70-72]

The treatment approach changes when considering FD. While in CD, psychoeducation is the main intervention, the management of FD (imposed on self) emphasizes the importance of establishing a treatment team in both inpatient and outpatient settings. Regular appointments are scheduled and a psychiatrist is consulted for further recommendations and a safety assessment. The clinician should treat authentic medical conditions and eventually discuss the diagnosis of FD as well as the rest of the differential diagnoses in a supportive manner, monitoring the clinician's countertransference, avoiding humiliation, and emphasizing that the clinician will be available for continuous medical care. It is recommended to treat other comorbid psychiatric conditions as well. On the other hand, it is relatively common for patients to react with anger, eventually leaving against medical advice or looking for another clinician. Supportive psychotherapy or CBT are the main psychotherapy modalities in these cases, but in those cases of FD imposed on another (usually a child or elderly person), the safety of the victim is the main priority, and it is mandatory to report to appropriate protective agencies.[52, 73]

Summary

Patients with Somatic Symptom and Related Disorders have higher medical care utilization and greater functional disability compared to non-somatizing patients. In DSM-IV-TR the key emphasis was that symptoms were not explained by a general medical condition but in DSM-5, the clinical focus relies on the level of impairment of daily functioning and distress due to the physical symptoms or health related concerns, regardless of existence of a medical explanation.

There are no FDA approved medications for any of the Somatic and Symptom and Related Disorders. Nonetheless, antidepressants seem to be moderately effective overall for unexplained physical symptoms, anxiety and depression in Somatic Symptom and Related Disorders.

Cognitive-behavioral Therapy (CBT) is considered the most effective evidence-based approach but other psychotherapeutic modalities have been helpful including but not limited to family therapy, supportive therapy, stress management, and psychodynamic psychotherapy. Psychoeducation has been emphasized for patients with Conversion Disorder. ❂

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Multiple-Choice Questions

9. **Which of the following DSM-5 Somatic Symptoms and Related Disorders diagnosis requires a medical workup?**

    A. Somatic Symptom Disorder

    B. Conversion Disorder

    C. Illness Anxiety Disorder

    D. Factitious Disorder

10. **Most patients diagnosed with DSM-IV-TR Hypochondriasis would meet the criteria for the following DSM-5 diagnoses:**

    A. Illness Anxiety Disorder

    B. Somatic Symptom Disorder

    C. Conversion Disorder

    D. Psychological Factors Affecting Other Medical Conditions

11. **The key feature of Illness Anxiety Disorder is that:**

    A. one or more somatic symptoms are required.

    B. it should last at least three months.

    C. patients always show care-seeking behavior.

    D. physical symptoms are not required for the diagnosis.

12. **Which of the following medications is FDA-approved for the treatment of Somatic Symptom Disorder?**

    A. Venlafaxine

    B. Duloxetine

    C. Escitalopram

    D. None of the above.

Best Practices in CME

Somatic Symptom and Related Disorders:
Overview, Updates, and Changes in the DSM-5

By Jin Y. Han, MD; Lindsay N. French-Rosas, MD; and Asim A. Shah, MD

ID#: L003366

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to all clinicians who require updated information regarding the epidemiology, pathogenesis, treatment options, and changes between DSM-IV-TR Somatoform Disorders and DSM-5 Somatic Symptom and Related Disorders. Studies find that patients whose focus primarily involves physical complaints experience less improvement, exhibit more disability, and utilize medical services more frequently.

Key Point 1: Functional Disability and Medical Care Costs

Patients with Somatic Symptom and Related Disorders have higher medical care utilization and greater functional disability compared to non-somatizing patients. This lesson will help clinicians become more equipped to deal with this oftentimes challenging patient population.

Key Point 2: Changes in the DSM-5

In the DSM-IV-TR, the key emphasis was that symptoms were not explained by a general medical condition. Conversely, in the DSM-5, the clinical focus relies on the level of impairment of daily functioning and distress due to physical symptoms or health-related concerns, regardless of the existence of a medical explanation. One exception to this, however, is Conversion Disorder and Pseudocyesis, where the workup will be sufficient to rule out the medical conditions.

Key Point 3: No FDA-Approved Medications

There are no FDA-approved medications for any of the Somatic Symptom and Related Disorders. Nonetheless, antidepressants seem to be moderately effective overall for unexplained physical symptoms, anxiety, and depression in Somatic Symptom and Related Disorders.

Key Point 4: Role of Psychotherapy

CBT is considered the most effective evidence-based approach, but other psychotherapeutic modalities have been helpful, including but not limited to family therapy, supportive therapy, stress management, and psychodynamic psychotherapy. Psychoeducation has been emphasized for patients with Conversion Disorder.

Notes

The Meaning of Despair: Existential and Spiritual Dimensions of Depression and Its Treatment

Larkin Elderon, MD; and John R. Peteet, MD

KEY WORDS: Depression • Spirituality • Religion

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) understand a conceptualization of the spiritual dimensions of depression, (2) assess for spiritual dimensions of a given patient's depression, (3) decide on an appropriate focus of treatment at the interface of depression and spirituality, which potentially may involve the coordination of spiritual resources, and (4) understand the ethical considerations associated with spiritually integrated care.

LESSON ABSTRACT: Depression is the most common mental affliction in the United States, with a lifetime prevalence of 17% and high rates of associated morbidity and mortality. Many studies have shown a correlation between spirituality and depression, most often noting an inverse correlation between spirituality and depression onset and/or severity. It is somewhat intuitive that spirituality and depression are closely related, given that depression often involves existential questions that are common to those of ordinary spiritual experience. Yet the integration of spirituality in the assessment and treatment of depression remains rare. This lesson provides a framework to understand the spiritual aspects of depression and outlines how one can (a) assess the role of spirituality in a given patient's depression and (b) involve patients' spirituality in depression treatment. A final section on ethical considerations discusses moral issues relevant to spiritually integrated care.

COMPETENCY AREAS: This lesson aims to help providers purvey patient-centered care, work with interdisciplinary teams, and grow in medical knowledge and professionalism as this lesson provides both a conceptual framework and practical approach to the complex relationship between spirituality and depression.

Introduction

Depression and Spirituality:

Major depressive disorder (MDD) is one of the most common mental health disorders in the *United States* (US), with an estimated lifetime prevalence of 17%[1] or higher.[2] In 2014, a national survey showed that 6.6% of all US adults had experienced at least one *major depressive episode* (MDE) in the past year.[3] Depressive disorders as a whole are currently the 11th leading cause of disability worldwide[4] and account for more disability days than any other illness in Americans aged 15–44 years.[5] Depressed individuals have higher rates of comorbid medical illnesses and tend to have worse outcomes with these illnesses than non-depressed individuals with the same illnesses.[6] Most victims of suicide, currently the eighth leading cause of death in the US, suffer from depression around the time of death.[7,8]

There is no doubt from these statistics that depression is a significant public health problem. As for most widespread illnesses, depression is complex not only in its ramifications but also in its origins and treatment.[2] For many patients, spirituality plays a role, perhaps in the etiology or protection against depression onset, and/or in one's experience of the illness and decisions on treatment. For instance, many depressed patients struggle with questions such as: *"Am I depressed, or lacking in faith?"; "Is life as unfair and empty as it seems?"; "Is God punishing me?";* or *"Should I take an antidepressant, or pray more?"*[9] In recent decades, literature has accumulated on various aspects of the connection between spirituality and depression, including the spiritual dimension of depression as experienced by those suffering from the illness,[10-12] evidence of spirituality as a risk and protective factor for depression,[13-15] the potential for spiritual growth in the face of adversity,[16] ways for depressed individuals to draw upon resources of a particular faith tradition,[17] frameworks to address spirituality in psychotherapy,[18-22] evidence for the effectiveness of spiritual interventions in depression treatment,[9,23-25] and even neuroanatomical correlates of spirituality and depression risk.[26]

Despite this literature on the association between spirituality and depression, the inclusion of spirituality in the assessment and treatment of depression remains rare.[14,27] Two commonly acknowledged reasons for this dearth of spiritual integration are a lack of provider knowledge of or comfort with the subject and ethical concerns. This lesson aims to educate providers on the topic by providing both a conceptual framework and practical approach to the complex relationship between spirituality and depression. **This lesson also discusses some of the common ethical challenges that arise when offering spiritually integrated care.** Further in-depth discussion on both topics can be found in Peteet's 2010 publication *Depression and the Soul: A Guide to Spiritually Integrated Treatment.*[28] Though spiritually may not play a role in all cases of depression, its potential prominence in the illness, in conjunction with the high prevalence of depression worldwide, makes this lesson broadly relevant.

Religion and Spirituality:

Definitions

Although an operational definition of the terms religion and spirituality remains elusive, religion usually refers to a tradition of beliefs, experiences, and practices shared by a community, whereas spirituality is a broader category that refers to a person's connection with a larger or transcendent reality that gives life meaning. By this definition, a person could be spiritual, but not religious, or religious, but not spiritual. Spirituality could include awe in the face of nature, or hope for immortality through a scientific intervention. It should be noted that even those such as atheists, who do not consider themselves at all spiritual or religious, have a philosophy of life or a worldview. Freud defined this worldview as "an intellectual construction which solves all the problems of our existence uniformly on the basis of one overriding hypothesis."[28, 29]

Prevalence

Just as depression is common, religiousness and spirituality are widespread in the general population. Data from 2010 estimate that 84% of the global population self-identifies with a religious group, while only 16% of individuals report no religious affiliation.[30] In a 2005 poll of US citizens, 88% of respondents described themselves as religious and/or spiritual, and only 7% stated that spirituality was not at all important in daily life.[31,32] Beyond the importance of spirituality to the vast majority of the population, multiple studies highlight the importance of spirituality to many aspects of life, including mental health.[32]

Understanding the Spiritual Dimensions of Depression

Spiritual Dimensions of Depression:

As Dan Blazer states, "Of all the psychiatric disorders, depressive disorders have been the most closely correlated with ordinary spiritual experience. The struggle with depression reaches to the very core of spiritual experience in many faith traditions. Depression is intertwined with the spiritual self."[33] Indeed, concerns relating to spirituality and concerns relating to clinical symptoms of depression often overlap, as shown graphically in Figure 1. **In *Depression and the Soul: A Guide to Integrated Treatment*,[28] Peteet describes a conceptual framework for this overlap. The model includes five existential domains relevant to both spirituality and clinical depression: identity, hope, meaning/purpose, morality, and autonomy with respect to authority.[28]** Each domain involves issues that most individuals (depressed or not) consider from time to time, perhaps more frequently when facing hardships. Characteristics of an individual's spirituality in each of the five areas may either confer risk of depression onset or poor prognosis, or provide resilience, serving as a buffer against depression. Consideration of these five categories, and of their respective depressive and spiritual concerns, can aid providers in patient diagnosis, formulation, and treatment. Below, we describe each domain in detail; Table 1 provides a summary for reference.

Figure 1:
Domains of Potential Spiritual Distress in the Clinical Setting

Clinical Concerns
related to symptoms and functioning

Existential/Spiritual Concerns
related to human existence within a larger context

Shared Domains
Identity, Hope, Meaning/Purpose, Morality, Autonomy/Authority
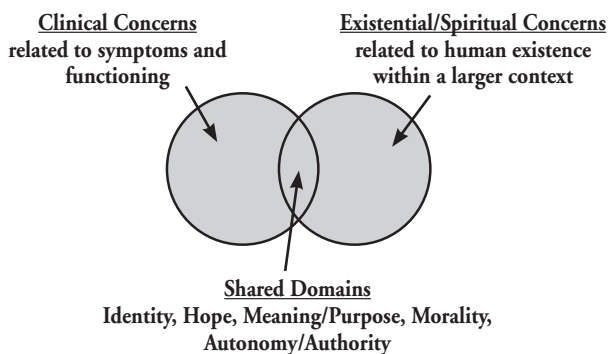
Identity

Individuals often question *"Who am I?"* or, when faced with hardship or misfortune, *"Am I still the person I was?"* Depression is likely to sway those with an insecure identity at baseline toward feeling doubtful and disoriented, leading to pessimistic responses to such questions. Spirituality in this domain has the potential to help an individual feel grounded in his or her identity despite adverse life circumstances. For instance, with the help of spirituality, a depressed individual may decide, *"this experience has helped me to see what I value most."* Or, *"I know I am worthwhile because God loves me."* This requires an engaged, transformative spirituality rather than one that is static. Transformative spirituality may be gained from a variety of sources. A few examples of the many potential sources include the Four Noble Truths of Buddhism or the Christian teachings of Jesus that one must lose one's life to save it. Regardless of the source, one can imagine how such spirituality, capable of grounding one's identity, could aid in resilience during depression or protect against depression before it occurs.

Hope

Anyone facing a great loss or misfortune may consider the question of what is yet to come and whether circumstances will improve. A hallmark symptom of depression is a lack of hope; individuals find themselves in a negative cycle of hopelessness, causing worsening mood, and vice-versa. Spiritually, hopelessness can be related to a lack of trust or loss of trust in a higher power. Either of these situations can be associated with significant despair and generalized mistrust. Individuals who place ultimate hope in ideals such as compassion, truth, or justice may have some protection against hopelessness, but they may also be vulnerable to despair if they feel they have demonstrated these ideals yet still face pain. In this domain, a helpful spirituality is one that is integrated, visionary, and able to sustain trust in a brighter future. This is in contrast to spirituality that is ambivalent or fragmented. As Judith Herman notes in *Trauma and Recovery*,[34] individuals who have endured trauma see the world in a fragmented manner. **She points out that an important goal in the recovery of a trauma survivor who has lost hope is to reconstruct an integrated worldview that can make trust and hope possible again.**

Table 1:
Domains of Potential Spiritual Distress in Depression

Domain	Questions in depression	Depressive characteristic	Healthy (non-depressed) characteristic	Healthy spiritual characteristic	Harmful spiritual characteristic
Identity	Who am I?	Doubtful, disoriented ("I'm not who I thought I was")	Grounded	Engaged, transformative (ground sense of identity by knowing oneself to be in a transcendent context, defining oneself in relation to a higher power)	Static (identity defined by worldly circumstances, unchanged by transcendent concerns)
Hope	Is it ever going to get better?	Despairing, mistrustful ("Life is hopeless")	Hopeful	Integrated, visionary (trust in higher power, find hope in one's worldview and knowing what comes after death)	Ambivalent (not sure whether one's greater power or worldview can be trusted to yield better circumstances in the future)
Meaning/purpose	Is life as empty as it seems? What's the point?	Aimless, lacking meaning ("Life has no meaning")	Visionary	Attuned, contemplative (find meaning in suffering as purifying, broadening, or redemptive)	Distracted (not considering the potential positive or constructive meaning of a depressive episode)
Morality	Is this my fault?	Guilty ("Events are my fault and I cannot be forgiven")	Forgiven	Mature, reconciled (recognize failures, accept forgiveness)	Developmentally delayed (guilt becomes irrational, magnified, and overwhelming; good and bad aspects of oneself cannot be integrated)
Autonomy/authority	Am I being rejected or punished by God?	Isolated, rejected ("I'm being punished/rejected")	Capable of intimacy/secure attachment	Accepted, loved ("Despite feeling depressed and even unloved, I know in my heart that God loves me")	Rejected/punished (trusting one's feelings of distance or isolation from the divine over one's faith in the divine)

Meaning/Purpose

All individuals tend to wonder about the purpose or meaning of life, but hardship and depression can turn this wonder into a struggle. An atheist facing a severe stressor such as illness may wonder whether his life has purpose. A trauma survivor may question the purpose of life if God allows such unspeakable experiences to occur. Depression is often associated with changes in mood and cognition that prompt an individual to wonder whether her life is worthless, in extreme cases leading to suicidality. Helpful spirituality in this domain is contemplative and attuned,

in contrast to being distracted, impulsive, or self-centered. Interestingly, both existentialists and researchers point out the importance of self-transcendence in finding meaning and purpose.[9, 35, 36] **An example of this can be seen in Buddhist meditation, in which those practicing meditation gain peace by finding perspective and a center of gravity outside oneself. Such attunement may similarly be directed toward prayer or worship of a divine being or, alternatively, toward music, art, or nature.** In this scenario, helping a patient to find and make meaning may be a goal of therapy.

Morality

Morality is perhaps more overtly related to spirituality than it is to depression or mental health. One's religion or worldview provides a guide to what constitutes a good moral decision and how to deal with moral failure (e.g., by. confession of sins, repentance, and forgiveness). Depressed individuals often struggle with guilt and may wonder if they are either to blame for, or are being punished by, adverse events. Here, a mature spirituality is needed. James Fowler, in *Stages of Faith*, described faith as having developmental stages just as do morality and a child's language or motor skills.[37] A patient who is developmentally delayed in this area, for example, thinking about God as a punitive authority figure from misunderstood Sunday school days, may need help to update his theology and values to become more mature. For instance, a therapist could help a patient in a troubled relationship weigh the value of intimacy against the more childish satisfactions of gaining control or needing to be "right."

Autonomy/Authority

Faith traditions differ in their beliefs as to whether an ultimate authority exists and, if so, what relationship with such a being is possible. Is there a divine being who can be trusted and who will love you despite your moral failures? Or, if you do wrong, will you be rejected and punished? Many depressed patients voice concerns that their suffering represents punishment or even abandonment by God. Isolation and a sense of general rejection by others are also common symptoms. For those who feel they will be loved and accepted regardless of their failures, attachment tends to be more secure both with the divine and with others, protective against depression. A therapist may help a patient examine her relationship with the divine as a first step to building more secure attachment.

Assessing the Spiritual Dimensions of a Patient's Depression

Determining the role of spirituality in a given patient's depression and what help the patient would like from a clinician entails taking a spiritual history. In recognition of its importance, the Joint Commission now requires a spiritual assessment for patients receiving care for emotional or behavioral disorders.[38,39]

Why Take a Spiritual History?

The benefits of gathering a spiritual history go beyond information collection and meeting requirements and extend to the provision of patient-centered care. A 2013 survey of outpatients in a psychiatry clinic revealed that one out of four patients wished for spirituality to be involved in care.[40] In general medical patients, 66% to 81% state that they would trust their physician more if she asked about *religion and spirituality* (R/S).[41] The inclusion of R/S discussions has also been shown to correlate with both improved doctor-patient relationships[42] and better adherence to prescribed treatment,[43] including adherence to follow-up appointments for patients with schizophrenia.[44]

Although some patients will decline the invitation to include spirituality in their care,[45] it is important for the provider to initiate the conversation. Many patients wishing to involve spirituality in their care may feel hesitant to present the topic due to fear of the provider's judgment or dismissal of the subject matter. To help alleviate these fears, inquiring into a patient's worldview should be undertaken with curiosity rather than judgment, including openness to a patient's declining to engage in a discussion of his worldview.

How to Take a Spiritual History:

It is helpful to begin a spiritual history with general, open-ended questions such as, *"Are you a religious or spiritual person?"* Alternatively, one may ask, *"Do you have a worldview or spirituality that you would like me to know about?"* This question recognizes that all patients have worldviews, whether or not these views fall into traditional categories of spirituality. If a patient denies that spirituality is important to her, this may be the end of the conversation. If the patient answers in the affirmative, questions should focus on how the patient's beliefs and/or practices (including community) may affect the patient's depression. This may involve exploring the existential domains discussed in the previous sections, identifying community resources available to the patient that may be of help, and discussing which treatments a patient is willing or unwilling to consider for himself. Useful background information can include ways that various faith traditions view depression and its treatment (see Peteet's

Depression and the Soul[28] and Koenig's *Spirituality in Patient Care*[38] for summaries).

Many screens and tools exist to aid in gathering a spiritual history; these have been well reviewed by Lucchetti and colleagues.[46] One of the most widely used screens is the FICA (faith, importance, community, and address). This tool prompts providers to ask about Faith or belief, the Importance of the influence of these issues in the patient's life, and the presence of Communities of support and, finally, to Address these issues in the context of clinical care.[47] Its advantages include brevity, as the screen can take only a few minutes to administer, as well as breadth, as the tool identifies several dimensions of spirituality for further discussion. Other commonly used tools and guidelines for taking a spiritual history can be found in a 2014 commentary by Moreira-Almeida and colleagues.[27]

As important as what one does to elicit a spiritual history is what one does not do during the process. In his 2004 article, "Taking a Spiritual History," Koenig summarizes for readers what to avoid, including prescribing religion in general, prescribing any specific spiritual or religious belief, forcing a spiritual history upon patients who do not wish for this to be part of their care, coercing patients to believe or practice in specific ways, and arguing with patients over religious matters.[48] Other authors note that in gathering a spiritual history, one should be aware of personal tendencies to either avoid R/S content and/or to overemphasize R/S content with patients.[49] These ethical issues are discussed further below.

It goes without saying that any assessment of a depressed patient should pay close attention to issues of safety and suicidality within the context of a full medical and psychiatric history (in which spirituality and religious beliefs about suicide may be important risk factors to assess).

Formulation:

The spiritual history should help the provider develop a formulation that integrates spirituality into a patient's diagnosis and treatment. This ideally involves (a) an empirically grounded description of the case that organizes key facts around a centrally important causal/explanatory source, (b) a focus on factors amenable to intervention, and (c) attention to the role of risk and protective factors in treatment.[28] The DSM-5 Cultural Formulation contains tools for formulating cases in a way that encompasses spiritual and cultural factors.[50, 51]

Determining the Appropriate Focus of Treatment

Once a provider has dealt with acute issues (i.e., suicidality, homicidality, psychosis leading to grave disability), determined how much a patient wants spirituality involved in his care, and formulated a patient's depression with spiritual aspects in mind, she faces the task of choosing an appropriate treatment plan.

Multiple approaches to spiritual care for depression have been identified and shown in empirical studies to have beneficial outcomes; these are described at greater length elsewhere.[28] To help providers determine the appropriate intervention or focus, we have provided a list in Table 2 of the existential domains discussed in Table 1 along with recommended treatment approaches for each.

For example, a patient with concerns centered on identity, who finds his sense of self is vulnerable to doubt or disorientation when depressed, may benefit from a humanistic emphasis on connecting with what most fulfills or best defines him. If religious, this could occur through grounding his identity in faith, i.e., in a relationship with God, through spiritual direction provided by a member of the patient's faith community.

Patients struggling with maintaining ultimate hope in the face of a world that appears fragmented, who may be vulnerable to mistrust when despairing, can benefit from help achieving a more integrated spirituality. This could take place through psychotherapy exploring unresolved trauma, through *cognitive-behavioral therapy* (CBT) bringing core beliefs more in line with experience, or through interpersonal therapy or spiritual direction, focusing on doubts in trusting God.

Patients looking for a sense of meaning and connection to a reality larger than themselves may benefit from meaning-centered therapy, mindfulness, and/or meditation. Mindfulness-based meditation, originally taught by Buddhists, is now commonly used in therapeutic venues such as *dialectical behavior therapy* (DBT) and *acceptance and commitment therapy* (ACT).

For patients struggling with guilt when depressed, forgiveness-promoting therapy can be helpful. A therapist may also find utility in employing positive psychology with its focus on virtues such as love.

Table 2:
Domains of Potential Spiritual Distress and Recommended Spiritually Oriented Treatment Approaches[a]

Domain	Depressive Concern	Healthy Spiritual Characteristic	Spiritually Oriented Approach
Identity	Doubt, disorientation	Engaged, transformative	Humanistic Spiritual Direction 12-Step Programs
Hope	Despair, mistrust	Integrated	Psychodynamic CBT Spiritual Direction IPT
Meaning/purpose	Meaninglessness	Attuned, contemplative	Meaning Centered Mindfulness Meditation
Morality	Guilt	Mature	Forgiveness-Promoting Therapy Positive Psychology
Autonomy/ authority	Isolation, rejection	Accepted, loved	Psychodynamic IPT Spiritual Direction

a CBT: cognitive-behavioral therapies; IPT: interpersonal therapy

Patients with existential concerns related to relationship to ultimate authority, who are prone to feel isolated or rejected when depressed, benefit from feeling loved or accepted by God. Clinicians can help them find or access resources for achieving this through their faith traditions using psychodynamic psychotherapy with a focus on distorted object relations. Interpersonal therapy or spiritual direction may also help them address problems in their relationship with God.

The above distinctions can be helpful in choosing a therapeutic focus and technique, though addressing concerns in one area can be expected to help address concerns in other domains. It should also be noted that, particularly for complex patients with multiple issues, one may begin therapy with a focus on one domain but then shift the focus as therapy progresses and new conflicts or value questions arise.[28]

Role of the Therapist:

Once the provider and patient agree on a focus of treatment, there are various options regarding the role of a therapist in spiritually integrated care. Peteet[28] describes four major approaches:

1. **The therapist acknowledges the spiritual issue but limits the discussion to strictly psychological or medical dimensions (i.e., addresses a patient's anger with God by examining the patient's relationship with authority figures in his or her life).**

2. **The therapist clarifies the spiritual and psychological aspects of the problem and suggests resources to address the former. This might involve referral to religious or spiritually-based CBT, a 12-step program, or a counselor with similar beliefs to those of the patient.**

3. **The therapist addresses the problem indirectly, using the patient's worldview within the treatment (i.e., explores how the patient could make better use of the resources of his or her own tradition, for example, by exploring the range of beliefs in a religious denomination).**

4. **The therapist addresses the problem directly, using a shared perspective. This approach may include prescriptive use of shared values, beliefs, or practices, i.e. meditation or scripture reading. Use of this approach requires careful attention to boundaries, transference, countertransference, and consent.**

The choice of an approach depends on the patient's wishes, the therapist's clinical assessment of which approach would be most relevant or helpful, and the therapist's comfort with incorporating spirituality. The fourth approach in particular raises ethical challenges, discussed below.

Coordinating the Provision of Spiritual and Clinical Resources:

For the second and third approaches described above, the mental health provider helps the patient to find and use spiritual resources. As discussed at greater length in Peteet's *Depression and the Soul,*[28] there are now many accepted models of treatment for individuals with depression with spiritual aspects, ranging from secular settings to those offered in faith-based settings. As this lesson focuses on how secular providers can integrate spirituality into their work, this section summarizes how faith-based care may play a role and how secular providers may help coordinate such care.

A number of models of faith-based care exist. Pastors, including Christian clergy and Muslim imams, provide much of the frontline counseling to individuals in their respective congregations.[28,52-54] Such leadership figures may alternatively refer patients to counselors of the designated faith. This experience is likely similar in many ways to seeing a secular therapist; however, the counselor will likely take on the fourth therapist role listed above. Alternatively, patients may see a pastoral counselor who might take on a more active role in leading the patient spiritually. Similarly, spiritual directors are trained individuals who help patients with the primary goal of enhancing faith rather than alleviating symptoms or distress.[55]

Many patients will engage in one or more of these counseling options in addition to seeing a secular therapist. When this is the case, communication among providers can be key to preventing the patient from receiving conflicting advice and to avoid splitting.* This can be particularly important, as many spiritual care providers lack formal training in transference or countertransference or in how to deal with traumatized or borderline patients.[28] Clinicians may also be called upon to provide psychoeducation, for example, if a patient is hesitant to take an antidepressant based on a faith leader's advice against this method of treatment.

Beyond individual counseling in the faith-based setting, many faith communities offer resources for mental health that are not identified as such. For example, spiritual practices such as prayer, meditation, and worship service may help patients develop and maintain a sense of meaning and purpose, while also building supportive relationships. Positive religious coping (experiencing God as being for one's needs rather than against them) can also be developed in faith-based settings without formal mental health intervention.[28] All of these are likely to move patients toward healthy spirituality, as depicted in Table 1. Though a secular provider should not prescribe any of these activities, it may be helpful to discuss with patients what resources are available to them in their community.

In summary, a mental health provider's role in arranging and participating in spiritual treatment varies and should be informed both by the provider's training and comfort, ethical considerations, and patient wishes. At the least, spirituality should be assessed and the patient should be educated on options to integrate spirituality into depression care if she so desires.

Clinical Case Example:

The following vignette provides one example of spiritually integrated care, as described in the above sections:

A 35-year-old woman presented with tearfulness, anxiety, and longstanding feelings of inadequacy. She had grown up compulsive about achieving high grades and maintaining a thin figure, in part related to external pressure to do so from her mother. She had always yearned for more closeness both with her mother, who was frequently preoccupied with anxiety, and with her father, a busy CEO. In college she began going to church and adopted faith as a central focus of her life. At the time she presented for psychiatric care several years later, she cited faith as important but noted that her church's sermons seemed judgmental and that she had begun to experience God as critical and distant.

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* Splitting in this case refers to a defense mechanism in which individuals tend to split people into polarized categories, e.g., viewing people as either all good or all bad. This defends against the more complex and potentially overwhelming reality that all people have both "good" and "bad" features. When patients split providers, they may idealize one provider while viewing another as useless. This is harmful to treatment as it may lead patients to irrationally reject a provider who would otherwise play an important role in his care.

The treatment plan included medication, supportive therapy, and insight-oriented therapy. By the patient's choice, there was a focus on spirituality; even in difficult times, she cited her faith as a source of identity and meaning. A discussion in therapy of how her core beliefs differed from the "you should" messages she heard weekly in church led her to explore other congregations. She came to value more personal intimacy with God and found a church that emphasized this. She remained prone to self-criticism and vulnerable to depressed moods when thinking about her weaknesses or failures. However, she also began to describe feeling "delighted in" by God. She noted that from God she found the care and closeness she had desired from her parents. Over a few years of treatment, she grew more open and forgiving toward herself, in part due to the emphasis of these values in her new church.

In this example, the therapist used a psychodynamic approach to help the patient with struggles regarding authority; the patient initially felt God was distant and critical but moved towards feeling loved and accepted. To address this spiritual struggle, the therapist incorporated the patient's spiritual strengths in the areas of meaning and identity; the patient had demonstrated faith that was contemplative, engaged, and transformative, all of which likely aided the patient's progress in therapy. The therapist also used CBT to examine core beliefs, helping move the patient from despair and mistrust to hope. This involved helping the patient find a church that was more in line with her beliefs. Without recommending a certain faith or faith community, the therapist guided the patient to make a choice based on her own beliefs and preferences. This would fall under the third of the four therapist roles described above. Depending on the patient's preferences, the therapist may have involved even more faith-based resources to aid the patient, for instance, suggesting that the patient consider engaging in spiritual direction or a church small group to provide additional support.

Ethical Considerations

Effect of a Clinician's Worldview:

Just as a patient's world view and spirituality color his experience of depression, a therapist's world view influences her approach to depression and to each patient. Abernathy and Lancia have usefully described the roles

of religiocultural transference and countertransference.[49] They suggest that providers be attuned to (a) their own degree of openness to or avoidance of R/S content, and (b) the meaning of their own R/S and how it affects their reactions to patients.

For the former, the authors note that all providers have a predilection to either over- or under-emphasize R/S in care and that it is important to determine to which category one belongs in order to avoid inappropriate inclusion or exclusion of the topic. Similarly, examination of one's own R/S current state and background, and observation of one's reactions to the patient's R/S beliefs, can be critical for understanding the patient and ensuring that any preconceived notions on R/S do not interfere with treatment.[49] For example, these may color how one decides if a religious patient is "hyper-religious."[28]

As another example of how these factors can come into play, consider the situation of a therapist who either agrees or disagrees with a patient's views. If the therapist shares the views of the patient, he may make assumptions about the patient's views and inadvertently leave important areas unexplored. If he holds views counter to those of the patient but feels the patient would benefit from adopting his, he may consciously or unconsciously encourage this. Whether the provider is from a similar or different background from his patient, understanding his own beliefs and how they affect the provider–patient relationship is key to providing ethical and quality care.

Boundaries and Self-disclosure:

A common question in providing spiritually integrated care relates to when it is appropriate to disclose one's own world view. First, it is important to understand a patient's request for such information, and how that information may serve the patient, as with any other request for disclosure.[56] In some cases, sharing one's own world view may be a critical part of informed consent, as a patient may wonder if he can trust a clinician. In other cases, the patient may be inquiring more for provocative reasons, perhaps in an attempt to steer the conversation off course.[28]

Further boundary concerns may arise when treating a patient of one's own faith background. These include the question of whether it is acceptable to treat a patient who is also in one's faith community and whether and/ or when it is acceptable to pray with a patient. Treating

an individual in one's own community creates a dual role that can make drawing appropriate boundaries more difficult and confidentiality more of a challenge to maintain. In this situation, one can see the importance of Gutheil and Gabbard's distinction between a boundary crossing, a descriptive term, and a boundary violation, which is harmful in nature.[57] Seeing a patient who is also in one's faith community may fall under the category of a boundary crossing, but if it is judged to do more benefit than harm, it may not constitute a violation. Similarly, most agree that it could be acceptable to pray with a patient if the patient so requests, if it advances rather than interferes with the treatment and if the provider genuinely feels comfortable doing so. However, prescribing prayer is generally considered unethical, even when working with a patient of one's own faith background.[28]

It should also be noted that if a provider feels that she cannot pray genuinely for a patient (i.e., if a Christian patient requests that an atheist provider pray for him), this may be a time for the provider to disclose personal information to explain her refusal. The amount of information disclosed generally need not and should not be extensive.[58]

Potential for Undue Influence:

As noted in the above sections, an examination of one's countertransference and reasons for self-disclosure is important in reducing the risk of promoting one's own faith beliefs, whether consciously or unconsciously. Though it should go without saying that this is unethical, the process of undue influence can be subtle. What may begin as an innocent discussion of spiritual topics may leave a patient feeling obligated to agree with a provider. It can also be tempting, given the research on the protective effects of R/S on depression, to encourage R/S to lessen a patient's illness. This is also considered unethical. By analogy, as Koenig notes, no clinician would want to inquire about marriage in a biased way, or suggest that a patient become married, simply because marriage correlates better with health than the single state.[59]

In this section, we have skimmed the surface of ethical challenges and considerations that may arise with the provision of spiritually integrated care. We urge clinicians to be aware of potential boundary crossings and violations, to seek supervision, and, whenever taking on the role of spiritual provider or self-disclosing personal beliefs, to carefully consider (a) why one is making this decision, and (b) the associated risks and benefits to the patient.

Summary and Conclusions

Given multiple studies showing a relationship between religion/spirituality and depression, and the existential domains shared by depression and spiritual experience, it is important for clinicians to consider how a patient's depression may be intertwined with spiritual concerns. Addressing these both within the therapy and through collaboration with faith-based resources requires an appreciation for the transference, countertransference, and ethical challenges involved. 〽

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Multiple-Choice Questions

13. **In the framework of spirituality and depression described in this lesson, a patient struggling with hopelessness would benefit from what kind of spirituality?**

    A. Integrated

    B. Self-centered

    C. Developmentally mature

    D. Transformative

14. **For an individual struggling with finding meaning/purpose, what might be an appropriate spiritually oriented intervention?**

    A. Interpersonal psychotherapy

    B. Psychodynamic psychotherapy

    C. Meditation, prayer, or worship of a divine being

    D. Positive psychology

15. **A patient comes to you with a history of trauma, and you are working with him to transform his view of the world from fragmented to whole. His Catholic faith is very important to him. In addition to seeing you, his secular provider, he also sees a pastoral counselor through his church. He sees the counselor on a weekly basis and initially found the sessions helpful, but more recently he has been complaining to you that his counselor is a terrible provider, in contrast to you, the *"the best provider I could ever imagine."* With patient consent, you reach out to the pastoral counselor. Of the options below, what would be the most reasonable discussion to have with the other provider?**

    A. Convey to the counselor that he/she is ill-equipped to care for this patient.

    B. Convey to the counselor that the patient should have only one provider, and that seeing both you and the pastoral counselor is damaging for the patient.

    C. Explain the concept of splitting and how it may affect patient care.

    D. None of the above; pastoral care is best kept separate from secular care.

16. **Which of the following statements is true about provider self-disclosure on religion and spirituality?**

    A. Providers should never disclose their faith.

    B. Providers may disclose their faith but should realize this is, by definition, a boundary violation.

    C. Providers should disclose their faith if asked but need not discuss the matter, as it is a patient's right to know this information.

    D. Providers may choose to disclose their faith when asked but should consider why and what end it will serve.

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Best Practices in CME

The Meaning of Despair: Existential and Spiritual Dimensions of Depression and Its Treatment

By Larkin Elderon, MD; and John R. Peteet, MD

ID#: L003367

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Depression is a leading cause of morbidity and mortality worldwide. Religion and spirituality are also important to the majority of the world population and have been shown to correlate both positively and negatively with depression and its outcome. Despite these observations, spirituality is rarely incorporated into depression treatment. In this lesson, we aim to equip providers to offer spiritually sensitive and, if indicated, spiritually integrated care, by discussing the spiritual dimensions of depression and their implications for assessing the spiritual aspects of depression, incorporating spirituality into treatment, and dealing with ethical considerations that arise throughout.

Key Point 1: Spiritual Dimensions of Depression

Key existential domains of overlap between spiritual experience and depression include identity, hope, meaning/purpose, morality, and relationship to authority. Depressive struggles in these areas may be important targets for therapeutic change.

Key Point 2: Assessing a Patient's Spirituality

Providers should initiate a spiritual history with every patient. For those patients interested in bringing spirituality into their care, a full history should be gathered. This allows providers to properly formulate the patient's depression, laying the foundation for spiritually integrated treatment.

Key Point 3: Focusing Treatment at the Interface of Spirituality and Depression

Based on factors including the patient's need and the clinician's experience, clinicians can choose among several possible roles in dealing with a patient's spiritual concerns. Helping patients bring spiritual resources to bear on their depression may involve a variety of psychotherapeutic approaches, as well as assisting them to access faith-based resources.

Key Point 4: Ethical Considerations

Spiritually integrated care raises various ethical concerns to which providers must attend, including issues of transference and countertransference, self-disclosure, and the potential for undue influence.

Notes

The Detrimental Impact of Maladaptive Personality on Public Mental Health: A Challenge for Psychiatric Practice

Michael Pascal Hengartner, PhD

No commercial support was used in the development of this CME lesson.

KEY WORDS: Review • Personality • Epidemiology • Psychopathology • Psychiatric practice • Public health • Personality disorders • Nosology

LEARNING OBJECTIVES: In this lesson, readers will: (1) review the impact of maladaptive personality traits on mental health and functioning, and (2) appreciate the importance of early assessment of personality disorders which may abate the effects of common co-occurring psychiatric disorders, and thus avoid the negative risk factors described in the lesson.

LESSON ABSTRACT: Experts in personality psychology and personality disorders have long emphasized the pervasive and persistsent detrimental impact of maladaptive personality traits on mental health and functioning. However, in routine psychiatric practice, maladaptive personality is readily ignored and personality traits are seldom incorporated into clinical guidelines. The aim of this narrative review is to outline how pervasively personality influences public mental health and how personality thereby challenges common psychiatric practice. A comprehensive search and synthesis of the scientific literature demonstrates that maladaptive personality traits and personality disorders, in particular high neuroticism and negative affectivity, first, are risk factors for divorce, unemployment, and disability pensioning; second, relate to the prevalence, incidence, and co-occurrence of common mental disorders; third, impair functioning, symptom remission, and recovery in co-occurring common mental disorders; and fourth, predispose to treatment resistance, non-response and poor treatment outcome. In conclusion, maladaptive personality is not only involved in the development and course of mental disorders but also predisposes to chronicity and re-occurrence of psychopathology and reduces the efficacy of psychiatric treatments. The pernicious impact of maladaptive personality on mental health and functioning demands that careful assessment and thorough consideration of personality should be compulsory in psychiatric practice.

COMPETENCY AREAS: This lesson aims to help providers grow in the knowledge of how personality disorders may impact the outcome and course in the treatment of common co-occurring psychiatric disorders—and if they are assessed and treated early, can increase the chances of better functioning and recovery in these disorders.

Introduction

Recently, a special series published in the Lancet[1] drew the mental health profession's attention to the frequently ignored diagnosis of *personality disorders* (PDs). In the introduction to their paper, Tyrer et al.[1] stress the relevance of PDs for both mental health policy makers and medical practitioners, and legitimately warn that this highly impairing and burdensome condition is too often overlooked in clinical practice. **Epidemiologic surveys have revealed that in the general population the median prevalence rate for any PD is about 10%;[2] in specialized psychiatric care systems, prevalence estimates rapidly rise to ≥50%.[3, 4] However, inspection of official clinical records of in- and outpatient services would provide a completely different picture, because PDs are markedly underdiagnosed by clinicians.[5, 6] As a matter of fact, the diagnosis seldom appears in official clinical records. Tyrer et al.[1] suggest that less than 5% of all hospital admissions are officially recorded with a PD diagnosis. This implies that most patients with severe personality pathology are primarily diagnosed with and treated for other, often secondary and subsequent, mental disorders.** Therefore, this review emphasizes ways in which maladaptive and pathological personality challenges routine psychiatric practice and why specific consideration of personality is warranted for the global provision and distribution of mental health services.

A comprehensive review of the adverse impact of personality on psychosocial functioning and mental health stringently needs to incorporate normal personality traits such as the Big Five, which comprise neuroticism, extraversion, agreeableness, conscientiousness, and openness.[7] The categorical PD conceptualization included in DSM-5[8] and ICD-10[9] lacks accuracy and adequacy, and there is clear evidence favoring a dimensional PD conceptualization over the existing system with its arbitrary categories.[10, 12] In the year 2007, in view of the upcoming DSM-5, the majority of PD experts, comprising clinicians and researchers, agreed that PDs are best viewed as personality dimensions and that the categorical system incorporated in DSM-5 and ICD-10 should be replaced.[13] In support of this view, findings from original studies,[14, 15] meta-analyses,[16, 17] and comprehensive reviews[18, 19] consistently demonstrate that

normal and pathological personality are different manifestations of the same underlying latent spectrum of general personality functioning. In particular, neuroticism closely relates to general personality dysfunction and shows substantial overlap with most PD diagnoses.[14, 17, 20] Since, a detailed account of the dimensional structure of normal and pathological personality is beyond the scope of this paper, interested readers are referred to Widiger and Simonsen.[19]

In order to draw a comprehensive picture of the relevance of personality for public mental health and psychiatric practice, a thorough evaluation of findings from personality psychology research is necessary, adding valuable information to the traditional psychiatric research on PD diagnoses. This is particularly true since PD diagnoses and pathological personality traits are best viewed as extreme variants on general personality domains. Thus, in this narrative review, I will outline the empirical research literature on the pervasive impact of both normal and pathological personality. My main objective is to provide a comprehensive review of the literature that is aimed at demonstrating why a thorough assessment of personality is indispensable for psychiatric practice. In order to cover a broad range of public mental health issues, I will focus on the following four major targets of psychiatric practice: first, social functioning; second, occurrence of common mental disorders; third, course and remission of psychopathological syndromes; and fourth, service use and treatment response. This review will not deal with neurophysiological and endocrine pathways that may account for the association between personality and mental health. Such a discussion is beyond the scope of this paper and is better suited to other specialties. Readers interested in the biological bases of personality are for instance referred to the review by Depue and Fu.[21]

Impact of Personality on Social Functioning

Personality has a significant impact on almost all areas of human life.[22] By implication, this review can only focus on a few aspects that I have chosen for their face validity and their implications for psychiatric practice. My review of the impact on social functioning will thus mainly touch on aspects of interpersonal and occupational

functioning. Both of these topics are known to influence public mental health and are of considerable relevance for mental health policy and psychiatric practice.[23-25]

First, with respect to interpersonal functioning, it has consistently been shown that normal personality traits substantially relate to relational ruptures, interpersonal conflicts, and separation or divorce. For instance, using data from a prospective longitudinal study, Donnellan et al.[26] demonstrated that neuroticism in particular had a significant negative influence on subsequent relationship quality. Jockin et al.,[27] using a genetic analysis of an adult twin sample, estimated that in women and men a remarkable proportion of 30 and 42%, respectively, of the heritability of the genetic vulnerability for divorce was accounted for by personality. **A meta-analysis of longitudinal studies confirmed that personality traits—specifically high neuroticism, low conscientiousness and low agreeableness—substantially predict divorce.[28] Moreover, several large epidemiological studies have shown that general personality dysfunction and PD diagnoses relate to social dysfunction, interpersonal conflicts, and separation or divorce.[29-31]**

Another consistently replicated epidemiologic finding is the association of personality pathology with low educational achievement, low income, and unemployment.[29, 32] Hengartner et al.[33] showed that PD traits significantly relate to various adverse occupational outcomes, such as severe conflicts in the workplace and dismissal or demotion. Correspondingly, there is ample evidence that PDs strongly increase individuals' risk for disability pensioning.[34] Research in personnel and organizational psychology supports these findings. For instance, Wille et al.[35] showed in a prospective longitudinal study over 15 years that maladaptive personality traits negatively relate to desirable work outcomes such as career and job satisfaction, whereas they positively predict adverse outcomes such as job stress. In a meta-analysis of occupational performance motivation, Judge and Ilies[36] confirmed the substantial association between personality and performance motivation as expressed by effect sizes of $r = -0.31$ for neuroticism and $r = 0.24$ for conscientiousness. In another meta-analysis, Salgado[37] likewise demonstrated that neuroticism and conscientiousness were valid predictors for job performance across various job criteria and occupational groups. Finally, using data

from the *Netherlands Mental Health Survey and Incidence Study* (NEMESIS), Michon et al.[38] showed that in persons with common mental disorders, baseline personality traits fully account for subsequent work impairment.

In conclusion, the studies outlined above emphasize the predominant role that personality plays as an independent risk factor for global functional impairment. A stable and supportive romantic relationship, a regular income, and a fulfilling job are important resources for psychiatric patients. Since maladaptive personality compromises these domains of social functioning, it poses a serious threat to psychiatric practice. Clinicians should thus be aware that maladaptive personality significantly impairs their patients' social functioning and that high scores on specific personality traits undermine powerful resources, which in turn has a negative impact on therapeutic progress and patients' wellbeing.

Impact of Personality on Incidence and Prevalence of Common Mental Disorders

Research on both normal and pathological personality has stressed the strong and consistent association between personality and the occurrence of mental disorders.[22, 39, 40] There is compelling evidence from two meta-analyses that specifically neuroticism and to a lesser extent also low conscientiousness (i.e., disorderliness and impulsivity) substantially relate to mood, anxiety, and substance use disorders. Low agreeableness (i.e., antagonism and aggressiveness) is associated with externalizing disorders and introversion specifically with internalizing disorders.[41, 42] Moreover, neuroticism constitutes a broad vulnerability factor for the co-occurrence within and between both internalizing and externalizing disorders.[43, 44] Thus, in sum, cross-sectional epidemiological studies provide compelling evidence that neuroticism in particular is strongly associated with the occurrence and co-occurrence of all common mental disorders as expressed by large effect sizes of $d > 0.8$ or $r > 0.5$. **Neuroticism is also the most important trait underlying general personality dysfunction and specific PD diagnoses.[14, 17, 20] It consistently follows that the severity of personality pathology as well as PD diagnoses substantially relate to co-occurring mood, anxiety, and substance use disorders[32, 45] and to the number of co-occurring**

mental disorders.[46, 47] However, correlation does not imply causation, which is why cross-sectional studies are of limited validity for aetiopathological models. Only controlled longitudinal designs provide predictive validity for a construct and allow drawing stringent causal conclusions.

The few longitudinal surveys that included PDs produced consistent results that corroborate the status of PDs as crucial risk factors for the onset of mental disorders. Using data from the Baltimore *Epidemiologic Catchment Area* (ECA) study, Bienvenu et al.[48] showed that baseline PD traits significantly predicted first-onset panic disorder and agoraphobia over the follow-up period. **The Children in the Community Study revealed that PDs in adolescence significantly increase the risk for anxiety disorders, mood disorders, substance use disorders, ADHD and other disruptive disorders, and various educational and social problems in adulthood.**[49, 50] **Finally, using data from the first and second waves of the** *National Epidemiologic Survey on Alcohol and Related Conditions* **(NESARC), Grant et al.**[51] **likewise found that baseline PDs predicted the subsequent 12-month incidence of mood, anxiety, and substance use disorders.**

Compelling evidence for a causal link also comes from normal personality research. In longitudinal surveys, neuroticism in particular demonstrated substantial predictive validity for the occurrence of mental disorders [for a comprehensive review on neuroticism, see Lahey].[52] In more detail, Kendler et al.[53] showed that neuroticism strongly predicts the risk for lifetime and new-onset major depression and that neuroticism considerably reflects the genetic liability to depression. In other studies, Kendler and colleagues consolidated the association between neuroticism and depression by reporting that neuroticism moderates the impact of adverse life events on major depression[54] and by demonstrating that the genetic liability to depression alters people's sensitivity to adverse life events.[55, 56] Moreover, longitudinal data from the Christchurch Health and Development Study[57] as well as from a prospective longitudinal clinical study with adolescent inpatients[58] showed that neuroticism prospectively relates to suicidal ideation and suicide attempts.

It is important to note that neuroticism by no means exclusively relates to conceptually overlapping constructs such as depressiveness or anxiousness, which are *per se* specific facets of neuroticism. Linking neuroticism exclusively to symptoms of negative affectivity might thus appear circular or redundant. However, the predictive validity of neuroticism is not at all restricted to affective disorders. For instance, Van Os and Jones[59] showed in a large birth cohort that neuroticism at age 16 increases the risk, whereas extraversion reduces the risk for subsequent schizophrenia in adult life. Data from the Prospective Zurich Cohort Study revealed that variance in the expression of subclinical psychosis symptoms as repeatedly assessed from age 20 to 50 years is predominantly caused by stable traits.[60] Moreover, the facets of neuroticism, here especially depressiveness, substantially relate to the latent trait underlying the occurrence of subclinical psychosis.[60] In another analysis of this prospectively followed cohort, Leeners et al.[61] found that in women the baseline personality facets of nervousness, aggressiveness, depressiveness, irritability, and openness increase the risk, whereas sociability reduces the risk for subsequent sexual difficulties with reaching orgasm. Finally, Turiano et al.,[62] using data from the *Midlife Development in the United States* (MIDUS) survey, showed that increases in neuroticism and openness predict progressive substance use, while increases in conscientiousness and agreeableness predict declines in substance use over time. In addition, in that particular study, conscientiousness was an important moderator of the effects that personality traits have on substance use.[62]

Thus, taken together, these findings clearly demonstrate that persons with maladaptive personality traits are at highly increased risk for the development of subsequent mental disorders and other psychological difficulties. As a consequence, these at-risk patients should be observed and followed carefully once they have entered the health care system. Prerequisite to this recommendation is of course a thorough assessment of personality in every single patient as early as possible in the clinical evaluation process.

Impact of Personality on Course and Remission of Psychopathological Syndromes

Focusing exclusively on the occurrence of mental disorders in the general population would draw an incomplete

picture of the pervasive impact of personality. The effect of personality on the course and persistence of already existing mental disorders, that is, the primary disorders for which persons are referred to mental health services, is presumably of even greater relevance for clinicians' primary considerations in routine practice. Since most clinicians principally record and treat mental disorders, but not underlying pathological personality traits, we deliberately focus on the literature on common mental disorders and not on the course and stability of PDs as primary targets of intervention. Readers interested in the treatment and course of PDs may consult reviews by Bateman et al.[63] and Newton-Howes et al.[64]

Moran et al.[65] demonstrated in a 2-year longitudinal follow-up study of patients with the primary diagnosis of psychosis that independent of other baseline covariates, comorbid PD increased the odds of attempted or completed suicide over the observation period by 87%. Data from the NESARC revealed that in the general population the prevalence of a PD diagnosis, in particular, antisocial, borderline, and schizotypal PD, significantly increases the risk of persistent and addictive drug use[66] which conforms with the impact of high neuroticism and low conscientiousness on substance use as detailed above [see Ref. 63]. A 10-year longitudinal study of psychiatric patients with major depression and/or dysthymic disorder demonstrated that among various baseline characteristics, Cluster B PD (predominantly depicting the domain of negative affectivity) was the only robust and independent predictor of suicide attempts at follow-up.[67] Massion et al.[68] showed that in patients with generalized anxiety disorder and social phobia, baseline PDs reduced remission rates by 30% and 39%, respectively, over a 5-year follow-up period. In another prospective, longitudinal study of patients with affective disorders, baseline severity of personality pathology significantly predicted persistent impairment in the social functioning of those patients over the 12-year observation period, even when baseline psychopathology was adjusted for.[69] Using the same data, Tyrer et al.[70] additionally found that baseline personality pathology significantly impeded the remission of anxiety symptoms at 12-year follow-up. Accordingly, the authors concluded that PDs may predispose to treatment resistance and chronicity of affective disorders.[70]

Thus, as stated in the preceding section, a well-conceived treatment planning for common mental disorders stringently needs to incorporate maladaptive personality traits. Only when personality has been taken into account and treated in a timely fashion (that is, as early as possible), can clinicians possibly prevent persistent drug use, long-term dysfunction, and a chronic course of illness. The evidence presented here clearly shows that patients with personality pathology have more severe, persistent, and recurring mental disorders than do patients without personality pathology. It is therefore crucial to consider the impact of personality right at the outset of clinical evaluations when different treatments are gauged (for instance, whether a patient should receive intensive case management or not).

Impact of Personality on Service Use and Treatment Response

In contrast to the findings related to aspects of course and persistency of psychopathological syndromes outlined above, this section introduces studies that provide evidence for the influence of personality specifically on service use and treatment response. **To begin with, it is important to stress that personality significantly interferes with health care utilization, which poses a serious issue for health economics and resources in mental health practice. For instance, using data from the MIDUS survey, a large epidemiological study demonstrated that in the general population neuroticism in particular relates to the increased likelihood of mental health service use.**[71] Findings from the NEMESIS confirmed the crucial role of neuroticism by demonstrating that this particular personality trait increases the use of both primary and specialized mental health care.[72] **In addition, in that same study, it was also shown that once entered into the mental health care system, patients scoring high on neuroticism make more repeated visits.** The authors argued that persons scoring high on negative affectivity (typically borderline patients) are vulnerable to stress and lack appropriate coping strategies, which is why they need intensive professional help.[72] Those conclusions conform perfectly with the findings by Kendler et al.[54, 56] detailed above on the interrelationship between neuroticism, stressful life events, and the occurrence of depression.

Finally, personality not only influences service utilization but also the efficacy of and compliance with mental health treatments. For instance, a large longitudinal clinical study with over 600 patients with major depressive disorder revealed that low neuroticism and high extraversion and openness predict response to both pharmacotherapy and psychotherapy.[73] Addressing a similar aim but using a completely different setting, which compared group vs. internet-based cognitive behavior therapy, Spek et al.[74] found that lower baseline neuroticism significantly predicts better outcomes in both treatments. Based on a comprehensive literature review, Mulder[75] noted that personality, particularly neuroticism, generally predicts worse treatment outcomes, but that this association is not unequivocally clear and apparently depends on the study design. In contrast to that rather cautious verdict, a meta-analysis of the effect of PDs on treatment outcome in depression corroborates the detrimental impact of maladaptive personality traits.[76] The robust result of this study revealed that concurrent PD doubles the risk for a poor treatment outcome in major depression across various treatments (pharmacological and psychological alone, or combined).

Newton-Howes et al.[76] conclude that "a diagnosis of personality disorder is not necessarily a poor prognostic indicator. These patients simply require treatment of both the personality disorder and the depression. This offers a challenge to clinicians. Despite our best endeavors patients with personality disorder remain one of the most difficult groups in psychiatric practice (p. 18)". There is not much to add to this concise statement except to reiterate that clinicians can avoid treatment resistance and poor outcomes only if, first, they are fully aware of their patients' underlying personality pathology, and, second, if personality is stringently included in the treatment plan. Moreover, clinicians need to consider that patients scoring high on the personality trait of negative affectivity (that is, excessive neuroticism and respective Cluster B and C PDs) lack adequate coping resources. These patients are thus highly vulnerable to environmental stressors and negative life events, which is why they need ongoing long-term treatment and thorough supervision.

Conclusion

The eminent studies summarized in this narrative review provide compelling evidence for the pervasive and persistent effect of maladaptive personality, in particular negative affectivity (i.e., excessively high neuroticism) and the severity of general personality dysfunction (as reflected by the diagnosis of one or more PDs), on a wide variety of clinically relevant adverse outcomes. Several renowned PD experts with profound knowledge of the scientific literature and with extensive experience in clinical practice, including Tyrer et al.[1] and Krueger and Eaton,[40] suggest that a thorough examination of personality should be a mandatory and integral part of clinical assessment, prognosis, and treatment planning. However, any reader with clinical experience will, unfortunately, have to admit that this suggestion is far from being followed in routine psychiatric practice. Too many mental health professionals still neglect the pervasive impact of overt personality pathology, and many professionals are even less aware of the covert latent personality traits that underlie manifest psychopathological syndromes. In this respect, I hope that this review helps to give maladaptive personality traits the clinical attention that they deserve.

Tyrer[77] posits that pathological personality is the cause of all severe forms of persistent and recurrent non-cognitive mental disorders. This narrative review, although far from being conclusive, provides compelling evidence in support of this hypothesis. The implications for psychiatric practice provided at the end of each respective section deliberately remind the reader of two major points. First, maladaptive personality, in particular the spectrum of negative affectivity, substantially increases the risk of severe psychopathological syndromes, and pervasively impairs functioning, treatment response, symptom remission, and recovery. Second, clinicians should adopt routine assessment of their patients' personality as early as possible in the clinical process and incorporate this important information in their treatment decisions. Having said this, it should also be acknowledged that the assessment of maladaptive personality and the diagnosis of PDs are not that straightforward as this review might suggest. In fact, the assessment of PDs poses a challenge to psychiatric practice on its own, because there is no accepted gold standard and each assessment method has

its limitations.[78] These difficulties are not only due to the inadequate classification of maladaptive personality in DSM-5 and ICD-10 but are also caused by the very intricate nature of personality traits and personality functioning.[79] Research in normal and pathological personality has demonstrated that the accordance between self- and informant-reports is rather modest,[80, 81] although both sources have considerable predictive validity and both provide unique information that is important to the understanding of personality traits and PDs.[10, 79-81] The overlap between personality and mental disorders and the impact of acute psychopathological symptoms on the assessment of personality make this demanding task even more difficult. Therefore, the general consensus is that a multiple-informant assessment over multiple time points is the most accurate method for both the assessment of personality traits and the diagnosis of PDs. For a thorough discussion of these methodological issues, the interested reader is referred to the literature.

Finally, although not the primary aim of this review, I would like to suggest that researchers should at least consider including a short personality assessment in their study designs. By doing so, they may come to see that personality independently accounts for many important associations in mental health research, even in domains where it was not expected. 🕮

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Multiple-Choice Questions

17. **Which of the following personality traits, in particular, has been linked to depression and to increased mental health service use in patients?**

    A. Neuroticism

    B. Extraversion

    C. Agreeableness

    D. Conscientiousness

18. **According to the lesson, epidemiological studies have shown that personality pathology is associated with all of the following, *except*:**

    A. social dysfunction.

    B. interpersonal conflicts.

    C. high academic achievement.

    D. unemployment.

19. **Although the correlation of personality disorders and common psychiatric disorders does not indicate causation, personality pathology substantially relates to co-occurring:**

    A. mood disorders.

    B. anxiety disorders.

    C. the number of mental disorders.

    D. All of the above.

20. **Which one of the following statements best describes the central learning point in this lesson?**

    A. The presence of personality disorders is the causative factor in the development of psychiatric disorders.

    B. Persons with maladaptive personality traits are at higher increased risk for the development of subsequent mental disorders.

    C. Personality assessment is not necessary when treating a co-occurring psychiatric disorder.

    D. None of the above.

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Best Practices in CME

The Detrimental Impact of Maladaptive Personality on Public Mental Health: A Challenge for Psychiatric Practice

By Michael Pascal Hengartner, PhD

ID#: L003368

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

This lesson reviews how pervasively personality influences public mental health and how personality thereby challenges common psychiatric practice. Maladaptive personality is not only involved in the development and course of mental disorders but also predisposes to chronicity and re-occurrence of psychopathology and reduces the efficacy of psychiatric treatments. The pernicious impact of maladaptive personality on mental health and functioning demands that careful assessment and thorough consideration of personality should be compulsory in psychiatric practice.

Key Point 1: Prevalence of Personality Disorder

Epidemiologic surveys reveal that in the general population the median prevalence rate for any PD is about 10%; in specialized psychiatric care systems, prevalence estimates rapidly rise to ≥50% however less than 5% of patients are diagnosed with personality disorders and are treated for secondary co-occurring psychiatric disorders.

Key Point 2: Assessment

Evidence shows that patients with personality pathology have more severe, persistent, and recurring mental disorders than do patients without personality pathology. Therefore a thorough assessment of personality in every single patient as early as possible in the clinical evaluation process is key to identify traits that may hinder the treatment of co-occurring psychiatric disorders.

Key Point 3: Prognosis

Studies show that persons with maladaptive personality traits are at highly increased risk for the development of subsequent mental disorders and other psychological difficulties. As a consequence, these at-risk patients should be observed and followed carefully once they have entered the health care system.

Key Point 4: Recommendations

Clinicians should adopt routine assessment of their patients' personality as early as possible in the clinical process and incorporate this important information in their treatment decisions. Although the assessment of PDs poses a challenge to psychiatric practice because there is no accepted gold standard and each assessment method has its limitations, a multiple-informant assessment over multiple time points is the most accurate method for both the assessment of personality traits and the diagnosis of PDs.

Notes

Treatment of U.S. Military Soldiers and Veterans: Basics of PTSD, Administrative Issues, and Cultural Competency

COL (ret) Elspeth Cameron Ritchie, MD, MPH

KEY WORDS: Military • Veterans • Healthcare systems • PTSD • Cultural competency • Medical boards

LEARNING OBJECTIVES: This lesson reviews the *Military Health System* (MHS) and *Veterans Health Administration* (VHA) systems of care, including the basics of eligibility for service members and veterans. Clinicians will review the updated definition of PTSD (posttraumatic stress disorder) and be able to utilize evidence-based techniques outlined in this lesson in the treatment of PTSD.

LESSON ABSTRACT: *Posttraumatic stress disorder* (PTSD) is now a major topic in the scientific literature and the media, especially after the many years of the wars in Afghanistan and Iraq. This overview briefly outlines the basics of prevalence, diagnosis, and evidence-based therapy and treatment in the context of the wars since 9/11. This review also covers some critical administrative and cultural competency issues and also focuses on how to engage veterans in treatment.

COMPETENCY AREAS: This lesson aims to address the gap in learning and help providers gain knowledge in the areas of patient-centered care, interpersonal and communication skills, and commitment to lifelong learning. Many providers do not understand how to approach and treat combat veterans with PTSD and related conditions. Evidence-based treatments exist, including medication, cognitive processing therapy, and exposure therapy. These interventions are very helpful for patients who can tolerate them, but many cannot. Upon the conclusion of reading this lesson, readers will have a better understanding of how to engage and treat combat veterans with PTSD.

Introduction

Posttraumatic stress disorder (PTSD) is a major topic in the scientific literature and the media, especially after 15 years of wars in Afghanistan and Iraq. This overview briefly outlines the basics of prevalence, diagnosis, and evidence-based therapy and treatment in the context of the wars since 9/11. The lesson also covers critical administrative and cultural competency issues.

Approximately 2.7 million service members have served in the conflicts since the planes dived into the Twin Towers and the Pentagon in the US on 9/11/2001. Estimates of the numbers of service members who have deployed to Iraq and Afghanistan and have PTSD range from 15% to 25%.[1-3] However, the numbers of diagnosed and treated PTSD cases are always lower than of those who report symptoms on anonymous surveys, probably related to active duty service members' concerns about their careers.

While over half of recent veterans seek care in the *Veterans Affairs* (VA) healthcare system, the rest do not. Many seek some services in both the civilian healthcare system and the VA. Others obtain healthcare through their jobs and educational (e.g., college and graduate school) clinic providers. Therefore, it is critically important that not only military and VA providers, but also civilian mental health clinicians, know how to recognize and treat PTSD.

PTSD does not occur solely in combat veterans, of course. The symptoms of PTSD also follow sexual assault, crime, and disasters. However, this lesson will focus on combat veterans. By combat veterans, we mean both active duty members and those no longer on active duty who have served in Iraq and Afghanistan, including those in the National Guard and reserves.

Treatment Guidelines

There are well-established guidelines for the treatment of PTSD, developed by the American Psychiatric Association and the *Department of Defense* (DoD) and the VA. These guidelines are often referred to as evidence-based treatments and will be summarized later in this lesson. However, there are many patients who are either unwilling or unable or do not respond to the evidence-based treatments.

While these patients are often called "treatment-resistant" or "refractory," it is also likely that the treatments are not engineered to be palatable to service members. There are many explanations for non-compliance: (1) unacceptable side-effects from medication; (2) difficulties with making frequent appointments, especially for the cognitive-behavioral treatments; (3) the distaste of many service members to re-live their trauma and/or talk about it; and/or (4) the stigma of seeking treatment. Thus, this review also discusses the more "refractory" patients, with a focus on how to engage reluctant veterans in treatment.[4]

Administrative Issues and Medical Discharges

Service members need to be physically and mentally fit for duty, according to various regulations.[5] If service members have a significant mental illness, they will usually be referred to a *medical evaluation board* (MEB) to determine whether they are fit for duty. If they are found to be unfit for military service, they may be medically discharged. They may also be medically retired, depending on the severity of their condition, which carries significant disability benefits. The medical/physical evaluation board, now called the *integrated disability evaluation system* (IDES), is a complex process.[6]

PTSD does not necessarily lead to a medical discharge. If service members respond to treatment, they may be found fit for duty. Alternatively, with actual practices varying according to the Service, they may be administratively discharged, without medical benefits from the Military Health System. However, they may still be eligible for care from the *Veterans Health Administration* (VHA; see below).

Many complex cases are usually referred to the medical evaluation board process. Service members may or may not want a medical evaluation from the board, which offers both benefits and potential shame.

There are, in general, two major drivers of seeking or not seeking treatment, in the author's opinion, based on extensive experience. Service members who want to stay in the military do not want to go near a mental health provider, as they fear losing their jobs. For example, Marines refer to a psychiatrist

or psychologist as the "Wizard," as he or she makes Marines "disappear."

However, those who are nearing the end of their enlistment, or are planning to retire, have many pressures to endorse PTSD symptoms. These include the financial benefits of medical retirement (often at 50% of their base pay), free medical care, and other benefits.

Most, but not all, veterans are eligible for care from the VHA. Eligibility criteria are based on a number of factors, which include: (1) type of discharge, e.g., honorable, general under honorable conditions, other than honorable, or dishonorable; (2) whether the condition is service connected; (3) length of service; (4) exposure to combat; and (5) income.

Cultural Competency

A central theme with the veteran population is that of cultural competency. If you are a civilian provider, how do you understand the military culture? How do you connect with the young, but combat-hardened, patients?

This is critically important with this population, who are often ambivalent about seeking treatment. A typical presentation is of a young man, who says, *"My wife said she would leave me if I do not get help."*

As a start in cultural competency, one of the simplest approaches is to ask the patient about his/her MOS (military occupational specialty), enquire about his/her basic and advanced training, and ask him/her when and where he/she has been stationed and/or deployed to war.

Learn what patients' military rank is or was, and ask how they want to be addressed. Some will prefer to be addressed by rank, others by their first name.

In general, it is best to start with understanding that the role of military service is for our recent veterans. They have volunteered for their military service, and generally are very proud of their time in the military. Today's combat veterans do not want to be seen as victims. Treat them as "battle-hardened" or maybe "battle-scarred." Respect their service.

Terminology and Healthcare Systems

Some notes on terminology: "Service" refers to the branch of service: the Army, Navy, Air Force, or Marines (which is actually part of the Navy). Correspondingly, the personnel are Soldiers, Sailors, Airmen, or Marines. The term "service members" refers to all of the military personnel.

The term "veteran" has several meanings. It usually means service members who are no longer on active duty. Reservists may transition between active duty and veteran status. The term "combat veteran" is used for both service members and those who are no longer on active duty, who have served in conflict zones, such as Iraq and Afghanistan, as well as the first Gulf War, Somalia, and other conflicts.

Active duty service members are those who wear the uniform full time and receive care, generally through the *Military Health System* (MHS). TRICARE covers both those who seek care in military hospitals and the provider network.

Reservists include many categories of reserve service members, as well as the National Guard. Reservists usually serve a weekend a month and two weeks a year, although there are many variations. The National Guard belong to their state and may be mobilized in the event of state emergencies or be called to action for war.

All reserve components have seen unprecedented deployments since World War II. Although their care may be complicated as they receive healthcare through the MHS while on active duty, they are usually not eligible for care when on inactive status. They may be eligible for care within the *Veterans Health Administration* (VHA) system if they have served in combat or met other eligibility criteria. Often they transition between the MHS, the VHA, and civilian healthcare organizations.

The MHS is separate and distinct from the VA's healthcare system. The MHS consists both of the direct healthcare system, offered by hospitals and clinics on military posts, and the purchased care system, commonly known as TRICARE. Technically they are all one system, but many differences in eligibility exist. Retirees and dependents can go to the direct care system, but only if there is space available. Often they are referred to

the purchased care system under TRICARE. (For more details on these health care systems, see 7.)

The Iraq War was initially called *Operation Iraqi Freedom* (OIF). Later, another term that was coined was *Operation New Dawn* (OND). Service in Afghanistan is usually referred to as *Operation Enduring Freedom* (OEF). Thus, these veterans are often called "OIF/OEF veterans."

But there have been many other conflicts in the last 20 years, including the first Gulf War (Desert Storm), Haiti, Somalia, and Bosnia. The latter three conflicts are often referred to as *Operations Other than War* (OOTW). In addition, there have been many humanitarian missions that service members have deployed to, such as the tsunami in 2004 and operations dealing with Ebola in West Africa. The latter are not considered combat operations, but they have produced their own share of trauma.

Current Definition of PTSD

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) is the 2013 update to the *American Psychiatric Association's* (APA) classification and diagnostic tool which, in the United States, serves as a universal authority for psychiatric diagnosis. (DSM-5, ref 8). PTSD used to be classified as an anxiety disorder (DSM-IV). The DSM-5 now includes PTSD with Trauma- and Stressor-Related Disorders. Although the new DSM-5 appeared in 2013, it was slow to be widely adopted. The MHS and VA were scheduled to adopt it on October 1, 2014. The implementation was uneven, but is now generally in place.

These changes are summarized as follows: DSM-5 criteria now identify the trigger to PTSD as exposure to actual or threatened death, serious injury, or sexual violation. The diagnosis of PTSD is currently based on 8 criteria from the DSM-5.

The first 4 criteria pertain to the "actual event" and must result from one or more of the following scenarios, in which the individual:

1. **directly experiences the traumatic event**

2. **witnesses the traumatic event in person**

3. **learns that the traumatic event occurred to a close family member or close friend**

4. **experiences first-hand repeated or extreme exposure to aversive details of the traumatic event**

The disturbance, regardless of its trigger, causes clinically significant distress or impairment in the individual's social interactions, capacity to work, or other important areas of functioning. It is not the physiological result of another medical condition, medication, drugs, or alcohol.

Symptoms that accompany PTSD should be present for 1 month following the initial traumatic event and include the following: re-experiencing, avoidance, negative cognitions and mood, and arousal:

- **Re-experiencing covers spontaneous memories of the traumatic event, recurrent dreams related to it, flashbacks or other intense or prolonged psychological distress.**

- **Avoidance refers to distressing memories, thoughts, feelings, or external reminders of the event.**

- **Negative cognitions and mood represents myriad feelings, from a persistent and distorted sense of blame of self or others, to estrangement from others or markedly diminished interest in activities, to an inability to remember key aspects of the event.**

- **Finally, arousal is marked by aggressive, reckless, or self-destructive behaviors, sleep disturbances, hyper-vigilance, or related problems.**

A study by Hoge (2014)[7] compared diagnoses of soldiers under DSM-IV-TR and DSM-5. In brief, about a third of the soldiers who met DSM-IV-TR criteria for PTSD did not meet DSM-5 criteria. Almost a third were in the opposite camp, meeting DSM-5 but not the older criteria. The main discrepancy is related to the new Criterion C, which separates avoidant symptoms from depressive symptoms.

Brief Discussion of Comorbidities

While there are a few service members who have "pure" PTSD, in the experience of most clinicians that is the exception rather than the rule. (ref. 2, IOM) For example,

insomnia may lead to drinking to try to sleep. Numbing and avoidance lead to relationship problems and, often, break-ups or divorce.

PTSD, *traumatic brain injury* (TBI), and related diagnoses have long been associated with each other, due to the common weapon of the wars, blast injuries. Service members wear protective equipment over their torso and a helmet. Thus, blasts have primarily targeted the lower extremities, and other less protected parts of the human body, including genito-urinary organs, the arms, and the face.

The physical stresses of military service, including wounds and injuries, contribute to musculoskeletal problems, with corresponding pain and disability. These musculoskeletal issues have led to service members to be treated with opiates, which of course can cause dependence and addiction.

In both military and civilian populations, many switch from legal opiates to illegal heroin. Moreover, service members, especially after discharge from the military, thus start a sad slide into substance dependence, unemployment, and homelessness. Unfortunately, death by heroin overdose is increasingly common.

There is also the question of missed diagnoses. For example, the anti-malarial agent, *mefloquine* (Lariam) has been associated with many psychiatric complaints and may be confused with PTSD or TBI.[9]

Suicide

Suicides among U.S. Army personnel have been increasing since 2004, surpassing comparable civilian rates in 2008. They peaked in active duty troops in about 2014,[10,11] but are still rising in reservists. Suicides are consistently highest among young white males, but have been rising in older ages and females as well.

The risk factors for suicide among active duty members are well-known, as data are systemically collected. These include relationship difficulties, financial and occupational problems, pain and physical disability, and access to weapons.[12]

Suicides among veterans are estimated at 22 a day.[13] Less is known about their risk factors than for those on active duty. Anecdotally, suicides among recent veterans have the same risk factors as active duty service members, (e.g., relationship issues and problems with the law). For older veterans, they seem to be related to depression and substance dependence, risk factors that are more similar to those among the civilian population.

Evidence-Based Treatment

There are two forms of evidence-based treatment from well-established guidelines for the treatment of PTSD, developed by the American Psychiatric Association and the *Department of Defense* (DoD) and the VA. These include (1) pharmacotherapy or medication and (2) psychotherapy. *Eye movement desensitization and reprocessing therapy* (EMDR) is also an evidence-based treatment, but is not widely used by psychiatrists in the US.

Medication:

Pharmacotherapy includes two FDA-approved *selective-serotonin reuptake inhibitors* (SSRIs), *paroxetine* (Paxil) and *sertraline* (Zoloft). However, most clinicians use a wide variety of SSRIs, with the choice depending on their side-effect profiles. For example, paroxetine is more sedating, which may be useful if insomnia is an issue.

Many other medications are also used off-label, including second-generation antipsychotics and other standard medications for sleep. *Prazocin* (Minipress), a blood pressure medication that decreases autonomic arousal, is very helpful for nightmares. It should be started at 1 mg at night and may be increased slowly up to two or three mgs, and theoretically to 10 mgs with cautions given to the patient about potential dizziness due to drops in blood pressure.

It is very important to inquire about sexual side-effects, especially with SSRIs. They can cause difficulties with erection in men, and a loss of libido in both sexes.

A number of second-generation antipsychotics, such as *quetiapine* (Seroquel), are also used for nightmares and PTSD-related paranoia. However, they may cause unacceptable weight gain and related aspects of metabolic syndrome. Therefore weight and lipid levels should be checked periodically.

Psychotherapy

The evidence-based psychotherapies include (1) cognitive processing therapy, a variant of cognitive

behavioral therapy, and (2) exposure therapy. The first one involves telling the combat-related trauma and re-framing the trauma. The second includes gradual re-exposure to the trauma. A variant of this includes "virtual therapy," a computer-aided re-exposure process. *Eye Movement Desensitization Reprocessing* (EMDR) is also an approved treatment, although not many psychiatrists use it. Many experts consider it another variant of exposure therapy.

Although these therapies have been proven effective in most of those who finish the course of treatment, many veterans do not finish the treatments. They may be unable or unwilling to tolerate the need to talk about the trauma and/or do the required homework. The drop-out rate is generally high.[14]

Select Populations

Approximately 15% of the military are female. At present, 15% of active military, 17% of National Guard/Reserves, and 20% of new recruits are women. The recent wars in Iraq and Afghanistan have engendered a growing population of female veterans seeking healthcare through the VA. Thus, women are among the fastest-growing segments of new VA healthcare users; as many as 40% of women returning from Iraq and Afghanistan may elect to use the VA.[15]

There are certain occupations that may lead to an increased rate of PTSD. Medical staff may have been exposed to horrifically wounded service members and locals. They also may have been involved with detainee medical issues. In addition, many service members, including individual augmentees and other reservists, were assigned to difficult detainee missions, such as at Guantanamo Bay and Abu Ghraib. In general, reservists may not have the support of a cohesive unit.

Moral Injury

The concept of "moral injury" is an existential condition, related to but different than PTSD, which is a medical diagnosis. In general, most authors conceptualize it as an insult caused either by the shame of killing, or the guilt induced by having fellow service members die, while one has survived. A feeling of being let down by the military or United States may contribute.[16] Although not well studied by the medical community, most agree that it is a corrosive condition that contributes to relationship difficulties and suicide.

I recommend asking the service members and/or veterans about whether they have heard about moral injury. I will often define it for them, and their eyes will flash in agreement. I then ask them if they want to talk about it. Often an outpouring of experiences will follow, either in that visit or another one.

Complementary and Alternative Therapies

There are many other treatments for PTSD, which are not discussed in detail here. They are anecdotally helpful, but are not yet scientifically validated in the medical community. They include the following:

- **Mindfulness and meditation**

- **Exercise**

- **Acupuncture**

- **Canine and equine therapy**

- **Art therapy**

- **Novel psychological interventions such as** *Accelerated Resolution Therapy* **(ART)**

- **Newer pharmacological interventions**

- **Transcranial magnetic stimulation**

- **Stellate ganglion block, an anesthetic technique for pain**

These are often received well by veterans, but we do not know which works for whom. We will discuss these in another review.

However, there is one caveat: I almost always recommend more exercise. Exercise helps with mood, hypervigilance, weight, and avoiding diabetes and high blood pressure. Sometimes a doctor's recommendation helps with motivation.

Conclusion

This lesson briefly outlines the military context, administrative issues, and treatment options for PTSD and related comorbidities.

When I work with veterans with PTSD, I describe three "buckets": medication, psychotherapy, and alternative treatments. I give them options and advise them that not everything works for everybody; we need to work together to find what works for them.

The veterans respond well to learning about all the options and being able to choose which will work for them. They usually agree to a recommendation of more exercise as well. ◲

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Multiple-Choice Questions

21. **What are evidence-based therapies for PTSD?**

    A. Selective-serotonin reuptake inhibitors

    B. Cognitive processing therapy

    C. Acupuncture

    D. A and B

22. **Why do combat veterans avoid therapy?**

    A. Shame

    B. Stigma

    C. Avoidance of talking about the trauma

    D. All of the above

23. **How can you engage veterans in therapy?**

    A. Ask them about their military service.

    B. Discuss how it was a mistake to go to war.

    C. Ask them about their "war crimes".

    D. Lecture them on smoking.

24. **The side effects of medications used to treat PTSD include:**

    A. sexual side-effects.

    B. weight gain.

    C. sedation.

    D. All of the above.

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Best Practices in CME

Treatment of U.S. Military Soldiers and Veterans
Basics of PTSD, Administrative Issues, and Cultural Competency

By COL (ret) Elspeth Cameron Ritchie, MD, MPH

ID#: L003369

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Posttraumatic stress disorder (PTSD) is now a major topic in the scientific literature and the media, especially after the many years of the wars in Afghanistan and Iraq. This overview briefly outlines the basics of prevalence, diagnosis, and evidence-based therapy and treatment in the context of the wars since the attacks against the US on 9/11. This lesson also covers some critical administrative and cultural competency issues. The main focus is on how to engage veterans in treatment.

Key Point 1: Cultural Competency

A central theme with the veteran population is that of cultural competency. If you are a civilian provider, how do you understand the military culture? How do you connect with the young, but combat-hardened, patients?

Key Point 2: Moral Injury

The concept of "moral injury" is an existential condition, related to but different than PTSD, which is a medical diagnosis. In general, most authors conceptualize it as an insult caused either by the shame of killing, or the guilt induced by having fellow service members die, while one has survived.

Key Point 3: Pharmacotherapy Treatment

Pharmacotherapy includes two FDA-approved selective *serotonin reuptake inhibitors* (SSRIs): *paroxetine* (Paxil) and *sertraline* (Zoloft). However, most clinicians use a wide variety of SSRIs, with the choice depending on their side-effect profiles.

Key Point 4: Psychotherapeutic Treatment

The evidence-based psychotherapies include (1) cognitive processing therapy, a variant of cognitive behavioral therapy, and (2) exposure therapy.

Notes

Meeting the Psychosocial Needs of Burn Survivors and Their Families

Shelley A. Wiechman, PhD

KEY WORDS: Burns • Psychosocial Needs • Burn Survivors

LEARNING OBJECTIVES: In this lesson, readers will: (1) have a greater understanding of the psychological needs of patients with burn injuries at each stage of recovery; (2) be able to match a nonpharmacological pain control intervention with a patient's coping style; (3) review the overall adjustment of both adult and pediatric patients with burn injuries.

LESSON ABSTRACT: A burn injury and its subsequent treatment is one of the most painful injuries a person can experience. Patients may undergo a lengthy hospitalization marked by surgeries and painful procedures; and outpatient treatment can last for years after discharge. This lesson will focus on the emotional needs of burn survivors at each stage of recovery. Recent research has focused on attempting to predict who will struggle with their emotional recovery and therefore need more intensive intervention. Current research indicates that the nature of a burn injury alone has little to do with how well a patient eventually adjusts. Adjustment to a burn injury appears to involve a complex interplay between the preinjury characteristics of the survivor, moderating environmental factors, the nature of the injury, and medical care. Psychological distress during and after hospitalization may be likely in cases in which emotional dysfunction preceded the burn injury. Once hospitalized for burn care, patients often experience transient emotional distress, independent of their premorbid status. Depression and anxiety symptoms commonly co-occur during the acute phase of recovery and may persist for the first year after discharge, but they do not occur at a higher rate in burn survivors relative to other hospitalized patients. Overall, for the majority of people hospitalized, a burn represents a painful but temporary disruption of their normal routine. After injury and treatment, they eventually resume normal preinjury functioning, which is largely independent of the burn area or location. However, for the subgroup of patients who have been found to experience long-term disruption in social, vocational, and physical functioning, services such as long-term psychotherapy, vocational counseling, and intensive outpatient physical rehabilitation are critical. The current direction in the field is focused on better screening tools to identify patients in need of more intensive intervention earlier on and more robust and widely available outpatient mental health services, particularly for patients in rural communities.

COMPETENCY AREAS: This lesson addresses the emotional recovery of patients at each phase of burn recovery. It is critical that physicians caring for those with burn injuries provide comprehensive, patient-centered care while addressing emotional challenges patients may face in the rehabilitation process.

Introduction

Approximately 500,000 people receive medical treatment for burn injuries each year. This is surpassed only by motor vehicle accidents, falls, and drownings.[1] About 40,000 of these injuries are severe enough to warrant inpatient hospitalization. The American Burn Association verifies hospitals that meet their criteria as regional burn centers, and 30,000 patients each year are treated at verified burn centers. About half of these hospitalizations are children or adolescents. There are 3,275 deaths annually from fire/smoke inhalation in the United States alone. This is down from 5,500 deaths just 15 years ago.[2] Demographics from U.S. burn centers show that the etiology of a burn injury is related to age. The most common type of burn injury is a scald burn, with children, the elderly, and the disabled being most prone to this type of injury. Male adolescents are most prone to suffer a burn injury due to risk-taking behaviors, such as playing with fireworks or gasoline. Certain occupations are at more risk for burn injuries, including construction workers, electricians, and workers in the food-service, chemical, or fuel industry.[2]

In the last 20 years, great advances have been made in the area of the successful physiological recovery of burn patients, which has significantly increased their survival rate. Unfortunately, research on the psychological needs of individuals who survive burn injuries has lagged behind and continues to receive inadequate attention. It is promising, however, that many burn centers employ social workers, vocational counselors, and psychologists as part of the burn team. This lesson will summarize the research on the psychosocial outcomes of patients with burn injuries, and offer guidelines for working with burn patients to meet their psychological needs. After studying this lesson, the stages of recovery, and the available treatment, the reader will have a greater understanding of the psychological needs of patients with burn injuries and the various options at each stage.

Burn Injuries

The size of a burn injury is expressed as a percentage of the total body surface area. Wound depth is determined by the elements of the skin that have been damaged or destroyed. Two broad categories are used to describe the depth of injury: partial-thickness burns and full-thickness burns. Partial-thickness burns are hypersensitive and can be more painful than deeper full-thickness burns. **Burn pain severity does not correlate with the size or depth of the burn.[3] Patients with superficial burns, as well as those with full-thickness burns, report high levels of pain.**

Hospitalization for burn injuries may vary in length from less than one week to several months, depending on the severity of the burn and the presence of other medical complications, such as inhalation injury. A general rule of thumb for the length of stay in a previously healthy patient is one day for every 1% of *total body surface area* (TBSA) burned. Of course, this is affected by any complications such as failing grafts or infections. The physiologic recovery of a burn patient is seen as a continual process that can be divided into three stages: (1) resuscitative/critical, (2) acute, and (3) long-term outpatient rehabilitation.[3] Each stage has a distinct medical, environmental, and physical context and presents the patient with a unique set of challenges. For clarity, the discussion of the psychological needs of burn patients will follow these three stages.[4]

Resuscitative/Critical Stage

Issues:

Severe burn injuries are almost always treated in surgical departments and, preferably, in multidisciplinary burn centers. The resuscitative phase typically lasts up to 72 hours after the burn injury and involves maintaining fluid balance, removing dead skin, and preventing topical infection. Patients with greater than 20% burns and/or with an inhalation injury are usually treated in the *intensive care unit* (ICU) during both the resuscitative and critical phase and may stay in the ICU for weeks. Characteristic issues in these initial stages include stressors of the ICU environment, uncertainty regarding outcome, and the struggle for survival. The environment of the ICU can be both overstimulating with its bright lights, machines, and multiple healthcare providers, and understimulating with the monotony of lying in a hospital bed, often immobile for weeks at a time.

Cognitive changes, such as extreme drowsiness, disorientation, and delirium, are common during this

phase and can severely impact recovery.[5,6] Not only does delirium increase the length of stay and increase the risk of complications, delirium can also be associated with a variety of poor outcomes, including long-term cognitive and functional deficits as well as increased morbidity and mortality once discharged. Delirium can be caused by infections, alcohol withdrawal, metabolic complications, and effects of high doses of medications. Those older than 65 are at an increased risk.[6] Many patients report that they do not remember this phase of their treatment. Patients may also be intubated (passage of an oro- or nasotracheal tube for anesthesia or control of pulmonary ventilation), which substantially limits direct communication.

Treatment:

In-depth psychological intervention during this phase is of minimal value. Even if patients do become more alert, focusing on past or future concerns may be counterproductive; their primary task during this phase is physical survival. Directly confronting issues related to the causes or ramifications of the injury can easily overwhelm coping resources that are needed for survival. Due to patients' fluctuating mental status, it is futile to try and teach new coping strategies at this phase. Clinicians should protect coping strategies that patients are already using. Patients should be encouraged to cope with the frighteningly unusual circumstances of the ICU through whatever defenses are available, even primitive strategies such as denial and repression. Supportive psychological interventions should focus on immediate concerns, such as pain and anxiety management and inspiring hope in patients. Nonpharmacological management of pain and anxiety is especially important, given the side effects of medications used to treat these symptoms.

Medical staff can also effectively intervene during this early stage of recovery by working with patients' family members. Understandably, family members may be anxious and distressed while observing patients undergo treatment.[7] Patients' coping ability is often influenced by cues received from significant others. The presence of family members and friends can promote a sense of familiarity in patients and can alleviate anxiety and agitation. However, family members should be encouraged to intervene in a supportive and limited manner. As family members express high levels of anxiety and stress, patients

may pick up on these cues and behave accordingly. It is important to help family members understand this effect and help them to convey a sense of hope and calmness that will encourage patients to reflect these emotions.

Intervention, including education and emotional support, might also be directed towards the staff during this phase of recovery. Educational support may include helping staff to distinguish between distress and the syndrome of depression in patients and helping them understand the transient nature of delirium. Further, it is common for medical staff to feel helpless and question their adequacy in the face of uncertain physical status. They may then project these feelings onto patients. More common, it leads to burnout and compassion fatigue among staff. Providing support to staff members and helping them to understand and deal effectively with these issues can help them to monitor and gain insight into these potentially counterproductive reactions as well as increase job satisfaction and retention.[8]

Acute Stage

The acute phase of rehabilitation begins after capillary integrity has been restored and diuresis (excretion of urine) has begun.[9] This phase of recovery focuses on restorative care and includes nutritional support, excision and grafting, and topical wound care. As cognition improves and patients become more alert during this phase, they are faced with very painful procedures, often with less sedation. Although patients are moved off of the ICU and to an environment that is more consistent and less intrusive, they still must undergo painful treatments. For example, it is the practice of many burn centers to debride (excise devitalized tissue and foreign matter from wounds) burned skin on a daily or twice-daily basis. Burn injuries that lack potential to heal on their own are treated with skin grafts. Physical and occupational therapies are an important part of this phase to help prevent scarring, maintain a functional range of motion, and prevent the overall deterioration of bodily organs from sustained hospitalization. The intense, daily physical rehabilitation that includes range-of-motion exercises and splinting can be an additional source of pain and anxiety. Finally, as patients become more alert and oriented during this phase of recovery, they are more aware of the physical and psychosocial impact of their injuries.

Sleep Disturbance:

A common complaint of hospitalized patients is sleep disturbance. The environment can be loud, patients are awakened periodically throughout the night to have pain medication administered or to have vital signs taken, and patients' mood and/or levels of anxiety can affect their sleep. Nightmares are common sources of sleep disturbance and can be due to pain medications or a result of the trauma itself. Sleep deprivation can lead to higher subjective pain ratings and a decrease in mood; therefore, it is important to treat this symptom. Informing patients that dreams are normal and typically subside in about a month can help allay concerns of abnormality and refocus patients' mental energy on other areas of recovery. Medication and relaxation techniques may also help with sleep disturbance.[10] Common medications include *zolpidem* (Ambien) and *trazodone* (Desyrel). A consult with the psychiatry service should be obtained for medication recommendations.

Psychiatric Disorders:

Distress is common among many patients hospitalized for burn injuries, but symptoms do not often reach diagnostically significant levels. Symptoms of both depression and anxiety start to appear in the acute phase of recovery. Rates of depression and generalized anxiety are similar to those found in other hospitalized patients; however, *acute stress disorder* (ASD) and *posttraumatic stress disorder* (PTSD) occur more frequently in burn patients than in other patients.[11, 12] A clear distinction needs to be made between ASD and PTSD. ASD occurs in the first month following a traumatic injury, and PTSD is then diagnosed if the symptoms persist beyond one month. The literature includes estimates of moderate depression ranging from 7–46%, general anxiety from 13–47%, and PTSD from 9–45%.[13] Unfortunately, methodological problems with these studies limit the conclusions that can be drawn; e.g., researchers studying depression have not usually distinguished between a clinical diagnosis of depression and depressive symptoms.[14] Typically, a burn patient's average self-reported symptoms fall in the mildly depressed range. This is not surprising given the number of physiological symptoms required in the assessment of depression. Many burn patients do not meet formal criteria for a diagnosis of depression since their symptoms

may not have been present for more than two weeks, and because it can be difficult to assess many of the symptoms in the hospital setting (e.g., finding enjoyment in activities). It is important that symptoms of depression are treated (behaviorally or pharmacologically), even if the patient fails to meet all criteria for a diagnosis of depression. Researchers have identified certain conditions in which depression is more likely to occur. Females with facial burns and high pain levels are more likely to have depressive episodes.[14, 15] Finally, a premorbid history of depression can also lead to an increased risk of depression during hospitalization.[16]

Studies of anxiety disorders are more methodologically sound and have distinguished between general anxiety, PTSD, and, ASD. The incidence of general anxiety among burn patients seems to be comparable to that found among other medical and surgical patients and seems to decrease over time. Patients experiencing PTSD typically have larger burns, more severe pain, and expressed more guilt about the precipitating event. In a study of 54 consecutively admitted burn patients assessed for PTSD, 63% of patients reported intrusive, recurrent memories of the burn event, but only 30% met full criteria for PTSD.[17] This suggests that replaying the traumatic event in one's mind is a common method of processing the trauma and does not necessarily lead to a diagnosis of PTSD. One study found an actual increase in PTSD as time progresses after hospitalization, from 35% at 2 months after discharge to 40% at 6 months after discharge, and 45% at 12 months after discharge.[18] Again, it is important not to overlook subclinical symptoms of posttraumatic tress in patients who do not meet full criteria for the disorder, as the symptoms are causing distress for the patient and can inhibit recovery.

Treating Psychiatric Disorders

A diagnosis of clinical depression is not common, but it is important to treat subclinical symptoms of distress and depression. Brief, supportive counseling may be helpful, but medications may also be necessary. When offering counseling to a patient, it is often helpful to normalize the patient's depressive symptoms and provide reassurance that symptoms often diminish on their own, particularly if the patient has no premorbid history of depression. Behavioral activation and positive activity scheduling

can also be a helpful approach. More in-depth cognitive behavioral therapy may be difficult if a person's mental status is compromised due to opiate medications needed for pain control. If depressive symptoms become severe enough that they are interfering with a person's ability to participate in physical and occupational therapies and do what they need to do to recover from their burn injury, a more aggressive treatment approach with medications may be needed. Common classes of medications used to treat depression are the *selective-serotonin reuptake inhibitors* (SSRIs). If a clinician feels that a medication may be helpful, he/she should consult the psychiatry service.

Acute stress symptoms can be thought of as a predictable psychological response to the abnormal stress of the burn injury. Many patients will experience acute stress symptoms while inpatients, but only about one third go on to meet criteria for a diagnosis of PTSD. We have found that an effective initial approach to treating ASD involves normalizing symptoms for patients, teaching some relaxation strategies, and helping them to understand the origins of their symptoms via the fight or flight response. Social support and providing the expectation that symptoms will resolve with time is also an important factor in treatment for ASD symptoms. Often, just knowing that there is someone to talk with about the accident and that what they are feeling is normal may be enough to help the symptoms subside. An approach combining normalizing symptoms and education may be the most effective treatment for many patients initially, but a combined counseling and medication treatment approach is helpful when symptoms do not abate after a short period.[19] SSRIs have been shown to be effective for the treatment of both depression and anxiety. The implementation of medication should be a joint decision between the patient, counselor, and psychiatry service.

PTSD following the abnormal stress of an assault has been treated successfully with various forms of exposure therapy. Foa, Hearst-Ikeda, and Perry[19] found a brief intervention program with treatment that included exposure, relaxation training, and cognitive restructuring to be effective in reducing PTSD symptoms in women who had been assaulted. The authors attributed treatment success to instituting treatment two weeks post-trauma, rather than immediately after the trauma. There has been no research to date on the effectiveness of this type of intervention on PTSD in burn patients. Yet, waiting several weeks after the trauma to institute any interventions, which should take place after a patient has stabilized medically, is a good idea with burn survivors as well. Treatment may need to be undertaken when the burn survivor is an outpatient.

Premorbid Psychopathology:

Recent studies focusing on the issue of premorbid psychopathology in patients with burn injuries show that the incidence of mental illness and personality disorders is higher in burn patients than in the general population.[16] **The incidence of prior psychiatric disorders is estimated to be 28–75%; the most common diagnoses identified in these studies include depression, personality disorders, and substance abuse.** These also document several ways in which prior psychopathology has an adverse impact on hospital course, including longer lengths of hospitalizations and the development of more serious psychopathology after a burn injury. Burn unit staff often make the mistake of trying to treat a patient's premorbid psychopathology during hospitalization. Certainly Axis I disorders such as depression can be treated as an inpatient if symptoms are causing distress for the patient; however, more complex disorders such as substance abuse and personality disorders cannot be treated during the inpatient stay. Referrals to community treatment programs should be made once the patient is ready for discharge to prevent the exacerbation of these disorders once the patient returns home. In the case of personality disorders, the only effective inpatient intervention is to create a detailed behavioral plan to manage any behavioral problems. For example, avoid opportunities for the patient to split staff by designating a person to communicate the treatment plan with the patient. Set clear behavioral expectations for the patient and inform him/her of the consequences of violating these expectations (e.g., no smoking privileges if the patient uses profanity with a nurse). Encourage nursing staff to ignore inappropriate behavior by leaving the patient's room and to reinforce any positive behaviors.[20]

Grieving:

A patient may also begin the grieving process at this phase and become more aware of the impact of the burn injuries on his or her life. A family member, friend, or pet

may have died in the accident. The patient may also have to cope with the loss of their home or personal property. In addition to these external losses, the patient may also grieve for the loss of his/her former life (e.g., job, mobility, physical ability, appearance). A classic article dispels common myths about coping with loss.[21] It is important that mental health professionals and other staff respect this grieving process and help patients to grieve in their own way and at their own pace. Social support is important during this time; not all patients will want to talk about their grief, but counselors can offer their service and let the patients choose their preferred coping strategies. The hospital chaplain may also be helpful during this time.

Pain Control During the Acute Stage

Sustaining a severe burn is one of the most painful experiences a person may have, yet typical burn care inflicts more pain than the initial trauma. Once or twice daily, patients have their dressings removed, necrotic skin debrided, and antiseptic agents applied. This process may continue for weeks or months. Ptacek, Patterson, and Doctor[22] indicated that the pain reported by a patient varies substantially from day to day, does not follow a uniform pattern between individuals, and is not related to the size of the burn injury. Burn patients experience two distinct types of pain: background pain and procedural pain. Background pain is experienced while at rest; it is more of a continuous, long-acting pain. Procedural pain is experienced during a medical procedure and is greater in intensity and shorter in duration. Patients report that procedural pain is excruciating, despite receiving morphine during wound care.[4] Interestingly, some patients report that procedural pain is easier to cope with because of its transient nature. Background pain, however, can tax coping resources because there is no clear end in sight.

Assessment:

The appropriate assessment of pain is the first step to providing adequate pain control. The methods of measuring pain can be physiological, behavioral, or by self-report. Physiological parameters include heart rate, blood pressure, respiratory rate, and oxygen saturation. Although it can be difficult to ascertain the relationship between these parameters and the level of pain, they can be useful for assessing pain in patients who are not able to communicate with staff. Behavioral measures include crying or grabbing the wound. Self-report measures enable patients to indicate their pain level and can be in the form of numbers, pictures, or questionnaires. No single measure is adequate to use with patients of all ages, so it is advantageous to have a wide range of assessment tools available.[23] It is important to keep in mind that anxiety over painful procedures can exacerbate pain levels; thus, it is important in your assessment to ascertain whether or not pain or anxiety is the prominent issue so you can treat it accordingly.[24]

Pharmacological Treatment:

The treatment of burn pain is divided into pharmacological and nonpharmacological approaches. Pharmacologically, opioid agonists are the most commonly used analgesics. These drugs include morphine, hydromorphone, methadone, oxycodone, and fentanyl. Although physical dependence is expected with prolonged use of opioids, *psychological dependency* (addiction) is rare in patients being treated for burn pain. Legitimate concerns regarding risks and side effects, as well as patient comfort issues, such as nausea and constipation, may limit the use of pharmacological interventions in burn care. One role of the clinician is to assure patients that taking opioid analgesics is not a sign of weakness and that fears of addiction are unwarranted. Opioid analgesics may be supplemented with other pharmacological approaches, including inhaled nitrous oxide and anxiolytics.[25] *Lorazepam* (Ativan; a benzodiazepine) has recently been found to lessen burn pain, largely by treating acute anxiety.[26]

Nonpharmacological Treatment:

Nonpharmacological pain control techniques include cognitive-behavioral interventions and hypnosis. In looking for effective techniques, it is important to determine a patient's natural coping style. Coping styles can be divided into two broad categories: approach or avoidance. Patients who approach a stressful situation are also known as sensitizers; in a medical setting, they tend to cope by focusing their attention on the painful procedure. Patients who avoid a stressful situation are also known as repressors. In contrast to sensitizers, they cope by turning their attention

away from a painful procedure. Both coping styles can be effective; and it is not likely that a person can adopt a new coping style during an inpatient hospitalization. Patients who are sensitizing can benefit from coping strategies that allow them to reinterpret the meaning or sensation of their pain or become actively involved in their care. **Patients with a repressing coping style are likely to benefit more from approaches that allow them to dissociate from their experience, such as deep relaxation and imagery. These two styles anchor opposite ends of a proximity of care continuum. Interventions should be matched according to patients' coping style.**

A brief description of some of the nonpharmacological interventions follows, starting with interventions on the repressor or avoidance end of the continuum and working through to the sensitizing end of the continuum.

Hypnosis/Imagery/Distraction

Hypnosis with burn patients is an appealing approach because it can be applied quickly, often with dramatic results. Patients in burn units seem to be unusually good candidates for hypnosis because they are emotionally regressed from trauma care, dissociated by virtue of sustaining a trauma, and motivated to comply because of their high levels of pain.[27] Hypnosis is best applied before a patient undergoes a painful procedure. Several controlled studies indicate that such an approach reduces reports of pain.[24, 28] Generally, children under the age of 6 do not have the cognitive skills to be able to benefit from hypnosis, but imagery is very effective in young children. It is important to note that hypnosis should only be implemented by psychologists, psychiatrists, or other mental health professionals who have received specialized training. A professional who has not been trained in other methods of pain control should not use hypnosis in this situation. Although hypnosis can be highly effective, it may not always be the best method and the professional must be able to recognize when other interventions would be more appropriate. Since pain serves as a protective mechanism for our body, hypnosis should not be considered when the etiology of the pain has not been established. Hypnosis is also contraindicated if underlying emotional problems (e.g., emotional instability, personality disorders, dissociative disorders) could be exacerbated.

Guided imagery is another effective avoidance technique that can easily be learned by nurses, aides, and child life specialists. It is most likely to reduce pain through relaxation and distraction during painful procedures. For children, video games, reading, or listening to music may also be effective distraction techniques.[23]

Hypnosis and distraction delivered via a virtual reality system can be very effective, as it increases the feeling of presence and absorption. Several studies have been done with both virtual reality distraction and virtual reality hypnosis with good success.[29, 30]

Progressive Relaxation

Relaxation has been effective for background pain and in helping reduce tension created in the hospital setting.[32] It may also be used for patients who have difficulty sleeping.[10] Relaxation can reduce tension and discomfort associated with medical procedures for both adults and children; however, use of relaxation for wound care has not been effective, as the intensity of pain may overwhelm efforts at relaxation.

Operant Techniques

Basic operant behavior principles, such as reinforcing good therapy performance and not reinforcing escape behaviors, are effective in burn patients, particularly with children. An effective operant conditioning plan can also help reduce residual pain behaviors. Reward systems can be used for wound care and difficult therapy sessions. A good plan will include determining what motivates the patient and what can serve as rewards (i.e. walks, time on the computer, movies, stickers, toys). Reinforcement should be given immediately following the painful procedure. Next, the clinician and patient can develop a schedule for wound care and other painful procedures so that the patient knows what to expect and when. Finally, during wound care, pain behaviors should be ignored and non-pain behaviors should be verbally reinforced.

Patient Information

As dealing with the fear of the unknown can be more difficult than dealing with reality, some patients cope better with more information. Information can be given to patients on the details of procedures, upcoming surgeries, and sensory information during wound care (e.g., "this

will sting," "this feels sticky"). Getting the child life specialist involved to help present information to children is important in this phase.

Reappraisal

Cognitive techniques such as reappraising a painful situation or procedure can be effective for patients who fall toward the approach end of the continuum.[32] Explaining to patients that the sensations they are feeling indicate healing and regeneration of viable tissue may help the patient reappraise and accept the pain.

Associating the pain with positive effects can make it more bearable; it is helpful for patients to learn to discriminate hurt from harm and understand that burn pain of great intensity is always temporary.[33]

Participation

For adults and children who cope by immersing themselves in a painful situation, allowing them to participate in their own wound care is important. This is particularly true for patients who like to be in control of their environment; simply being in the hospital takes away control and requires dependency. Allowing patients to determine their schedules and to perform as much of their own wound care as possible is important and may reduce their perceived pain by minimizing the uncomfortable nature of the environment and helping patients regain a sense of control over their body.

Quota System

Patients who experience prolonged hospitalization may begin to develop a syndrome of helplessness (similar to the "learned helplessness" coined by Seligman[34] that is marked by withdrawal, passivity, and anxiety. The quota system is an approach to treating the helplessness phenomenon that has been successfully used in the rehabilitation and chronic pain fields.[35] The goals of this approach are to help patients gain a sense of predictability and control while, simultaneously, minimizing the overwhelming nature of rehabilitation through systematic, gradual increases in expected behaviors. The quota system begins with the taking of baseline measures for 3 to 5 days before the program is implemented. Targeted behaviors (which must be quantified and observed) can be any tasks that the patient feels are difficult or overwhelming. Common examples include sitting tolerance, walking, range-of-motion exercises, pressure garment use, and splint use. During the baseline phase, the patient is asked to perform the targeted behavior to the point of weakness, fatigue, or pain. The baseline is the average level tolerated during the 3-to-5-day period and serves as the basis for determining the initial value in the program. To promote early success, an initial value is chosen that is slightly lower (20%) than the average baseline performance. The number of the exercises done is then increased each day to a new quota by consistent, predictable, attainable increments (5–10% of the initial value) so that increased tolerance is built gradually. The patient is not allowed to exceed any of the quotas even if he or she feels capable of working beyond tolerance. Ehde et al.[36] reported the success of this approach on the burn unit.

Long-Term Rehabilitation

The long-term stage of recovery typically begins when patients leave the hospital and begin to reintegrate into society. For patients with severe burns, this stage likely involves continued physical rehabilitation on an outpatient basis, along with the possible continuation of procedures such as dressing changes and cosmetic surgery. As healthcare changes, more and more patients are being discharged earlier with open wounds and larger burns, and they are being cared for on an outpatient basis. This makes ongoing outpatient support for both physical and emotional issues even more important. Outpatient providers should screen for both anxiety and depression and make referrals to outpatient providers as needed.

Studies have shown that the first year after hospitalization is a psychologically unique period of high distress.[12] This is typically a period when patients slowly regain a sense of competence while simultaneously adjusting to the practical limitations of a burn injury. Patients face a variety of daily hassles during this phase, such as compensating for the inability to use their hands, limited endurance, and severe itching. Scarring can also create significant difficulties for patients during this time; even a burn injury that has been grafted has the potential for scarring. Burn injuries at any joint have the potential to result in impaired mobility. As scar tissue covering a joint contracts, flexibility is increasingly compromised.

Splinting, vigorous stretching therapies, and surgical releases are often necessary to maintain mobility. Severe burn injuries can also result in amputations, neuropathies (diseases of the nervous system, especially cranial or spinal nerves), and heterotopic ossification (calcification of the joints that can impair range of motion). [37, 38]

All these complications can result in permanent disfigurement and have an emotional and physical effect on patients, regardless of the size or location of the burn injury.[39] In addition to the high demands of rehabilitation, patients must deal with secondary stressors including family strains, return to work, and disruptions in daily life. A significant number of people may also continue to have vivid, distressing memories of the accident. Any symptoms of depression or anxiety disorders should be treated. Many of the symptoms that escalate in the first year after a burn injury may be transient symptoms of anxiety and depression which tend to decrease after one year post-injury.[12] In addition, there is evidence of improvement over time in adjustment to burn injuries, quality of life, and self-esteem, independent of the size of the burn injury. For a small number of patients, distress continues after one year; these patients should be diagnosed and treated accordingly. There has been very little research conducted on specific treatments for anxiety or depression with patients with burn injuries. Most clinicians will rely on standard treatment approaches for depression and anxiety, including cognitive-behavioral therapy and medications. Predictors of lower quality of life after one year post-injury include a limited range of motion and lasting decreased functional capacity, as well as problems with noncompliance during hospitalization and reliance on avoidant coping styles. Social support has been found to serve as an important buffer against the development of psychological difficulty.[40]

Vocational Adjustment:

Patients often undergo significant outpatient recovery before being able to return to work. One year post burn injury, about 75% of patients have returned to some form of work. [41, 42] Some patients choose to change jobs, but others experience undesirable changes in employment status such as a job reassignment or reduced work time. Approximately 50% of burn patients require some sort of change in job status.[8] Barriers to returning to successful employment within the first year after an injury include open wounds and physical limitations. In patients who have not returned to work after a year, emotional and psychological barriers were identified.[41] As expected, patients who sustained larger burns take significantly longer to return to work.

Although no studies have been conducted to date, our clinical experience has shown that the sooner burn survivors return to work, the better their adjustment and satisfaction with life. Of course, they may need to start gradually at a limited capacity, and if they were burned on the job, they may need counseling or support to overcome any anxiety or fears they have regarding their injury. Success on the job can increase self-esteem and reduce levels of depression, and it can also be an important part of physical and occupational therapy. When patients do not return to work, they are less active and become deconditioned. Given the importance of returning to gainful employment and the challenges that many burn survivors face, a vocational counselor is a valuable member of the outpatient burn team.

Body Image:

Patients who develop burn scars often report diminished satisfaction with their appearance and a lowered self-esteem.[43] One study looking at three-year trajectories of recovery in young adult burn survivors found poor perceived appearance was prevalent and persisted across the three years. Compared to non-burned peers, this body image dissatisfaction limited their social function.[44] There are several programs that have been developed to address these important issues. Both the Phoenix Society's BEST program and The Changing Faces program in Great Britain have been successful at enhancing self-esteem.[45] These programs include a hospital-based image enhancement and social skills program, along with a series of publications for patients that deal with aspects of scarring. The image enhancement programs focus on methods such as corrective cosmetic techniques, color analysis, and clothing coordination. Behavioral and social skills training can help the burn survivor develop practical communication strategies to deal with difficult social situations, such as staring, and can help prevent social isolation.[45]

It is critical that outpatient burn clinics have a mental health provider to address the ongoing emotional needs of burn survivors. Ancillary resources such as

support groups and peer counseling by burn survivors can also be important services. The Phoenix Society has an extensive aftercare program for burn providers and burn survivors that includes an online support group, a peer support program called SOAR, and a school reintegration program called The Journey Back. Burn centers should familiarize themselves with these programs and encourage patients to access these resources. Both the SOAR program and The Journey Back are hospital-based and provide curriculum and training for burn providers to assist with peer support and community reintegration. Major burn centers ideally have a network of burn survivors who are willing to go through the peer support training and talk with patients either in the hospital or after discharge. Peer counseling can be particularly helpful for burn patients who have had little exposure to, or inclination to work with, mental health professionals. Support groups for patients and family members, either on an inpatient or outpatient basis (or both), can also be immensely helpful.

Pediatric Burns

Family Issues:

Because over half of the burns in the United States occur in children, there are issues specific to the pediatric population that should be highlighted. First, the family becomes even more important when dealing with pediatric patients. Often, interventions are directed at the parents to teach them to participate in wound care and therapies. Because parents are vital to the burn care and rehabilitation of their child, parents are often encouraged to engage in their own self-care and to pursue therapy to treat any PTSD symptoms or guilt related to the burn injury. Although parent training may also be indicated, not all parents will be receptive to this intervention. The hospitalization of a child is a very stressful experience for families and parents may be too overwhelmed for any intensive therapy. However, it may be a good opportunity to teach parents about burn and injury prevention, to educate them about disorders such as ADHD, and to make referrals to community support agencies who can aid parents by providing supervision of the child or outpatient counseling.

Treatment:

Pain Control

As with adults, pain control will be a primary issue. Children experience the excruciating pain involved in acute burn care just as adults do. Unfortunately, young children do not have the cognitive capacity to understand the necessity for daily wound care. Historically, children have been under-medicated for pain. There are several probable factors, including caution on the part of the medical staff not to overdose narcotics, and a child's inability to verbalize when in pain or to request pain medications. Behavioral indicators such as crying, avoidance, withdrawal, and fear should be used to determine if a child is in pain and not properly medicated. The nonpharmacological interventions described earlier in this lesson have been found to be effective in reducing pain in children, and can be extremely important adjuvants to standard pharmacological analgesia. Children have the same range of coping styles as adults and should be involved in their care, with consideration as to what is age appropriate. For example, even two year olds can help wash themselves (if they have more of an approach style, or can blow bubbles if they are avoiders).

Behavior Plans

With pediatric burn patients, a thorough developmental history is crucial to prepare a good behavior plan, which should be implemented to avoid any anticipated behavior problems. These behavior plans should address the specific needs of each individual, including attempting to mimic the home schedule of the patient, as well as implement similar behavioral expectations that they are accustomed to at home. The basic component of a good behavior plan is to build in predictability, routine, and control over the child's environment. This includes:

- **Having a primary nurse assigned to work with the child.**

- **Creating a consistent schedule so the child can prepare for treatments and therapies.**

- **Having clear expectations/rules.**

- **Enforcing logical consequences when rules are broken.**

- **Providing considerable positive reinforcement for good behavior or getting through, e.g., wound care and therapies.**

- **Providing limited choices for the child (2 or 3 options) that can enhance the child's control over his/her environment.**

Consistency among the staff is important in implementing the behavior plan. Having a behavioral plan for a young inpatient can also aid parents in their attempts to establish a normal routine and environment once the child returns home. If the child is spoiled unnecessarily in the hospital, free of schedules and rules, then his/her behavior becomes that much more difficult to control upon returning home. Children's behavior may regress while they are being treated on an inpatient basis. For example, toddlers who were previously toilet trained may require diapers, and older children may have periods of enuresis (involuntary loss of urine). These regressive behaviors are not predictive of future behavior or adjustment.

Post-Trauma Adjustment:

There is little consensus concerning adjustment in pediatric burn patients. Most studies have failed to assess premorbid psychopathology, and it is thought that the measures available are not sensitive enough to detect the underlying distress that many pediatric burn survivors and their parents are reporting. Although few patients meet full DSM criteria for disorders, 10% to 50% of patients will show symptoms of distress, typically symptoms of anxiety or depression that include sleep disturbance, nightmares, poor appetite, and an exaggerated startle response. Recent studies have looked at recovery curves in children following a burn injury. Kazis et al.[46] used the *Burn Outcomes Questionnaire* to track recovery curves of preschool children with burns compared to non-burned children on various domains of function. Much like that of adults, they found significant improvement in almost all domains in the first two years after injury, particularly in the first six months after discharge. Despite the improvements, by five years post burn, most children did not reach the level of their peers in the domains of play and gross motor tasks. Parental worry also remained high, again indicating the need for interventions for parents. However, children with burn injuries actually surpassed those of their non-burned peers in the domains of language, emotional behavior, and family function.

When looking at rates of psychiatric disorders in adolescents who have a burn injury, the literature shows anxiety disorders to range between 35% to 40%, followed by substance use at 18% to 20%, and disruptive behavior disorders around 15%. These rates are low when compared with parental reports.[47] When we look at young adults who were burned as children, we find that the majority of young adult burn survivors are doing well compared to their peers; however, they do report higher levels of anxiety and lower self-esteem and self-perception, particularly around new groups or strangers.[48]

There do seem to be fewer problems with adjustment than anticipated or expected by investigators. Patients' age, stage of development, and relationship to their primary caregiver all influence reactions; patients' adjustment also plays an important role in how children adjust psychologically to a burn injury. The time since the burn injury seems to mitigate maladjustment; in other words, distress symptoms decrease significantly one year after the injury. Regardless of what the research shows, it is important not to ignore the symptoms of distress and to provide appropriate treatment.

Return to School

Returning to school will be a primary issue for children. After discharge from the hospital, many children need to wear splints and pressure garments to school. One study showed that children return to school an average of 7 days after discharge and miss an average of 22 school days. The study also noted that children had relatively little loss of function and did not suffer academically. As expected, children with problems in school before the burn injury had problems after the burn injury.[49, 50] The return to school can be facilitated with school reentry programs, such as the Phoenix Society's Journey Back program, close partnership with the school to establish reasonable accommodations and expectations, and written materials to prepare school administrators and classmates for the patient's return.

Summary

A burn injury and its subsequent treatment is one of the most painful injuries a person can experience. Patients may undergo a lengthy hospitalization marked by surgeries and painful procedures, and outpatient treatment can last for years after discharge. Yet, the emotional needs of patients with burn injuries have long been overshadowed by the emphasis on survival. Early outcome studies were often driven by medical models that assumed that the nature and size of a burn injury would predict its emotional impact. Consequently, powerful determinants of emotional outcome such as preinjury adjustment or social support were often ignored. Current research indicates that the nature of a burn injury alone has little to do with how well a patient eventually adjusts. Adjustment to a burn injury appears to involve a complex interplay between the preinjury characteristics of the survivor, moderating environmental factors, the nature of the injury, and medical care.

Psychological distress during and after hospitalization may be likely in cases in which emotional dysfunction preceded the burn injury. Once hospitalized for burn care, patients often experience transient emotional distress, independent of their premorbid status. Depression and anxiety symptoms commonly co-occur during the acute phase of recovery and may persist for the first year after discharge, but they do not occur at a higher rate in burn survivors relative to other hospitalized patients. Delirium, which is usually confined to the critical phase of recovery, and PTSD or ASD symptoms, which may persist during the acute phase and after discharge, are more commonly seen in burn patients and can have long-term effects. Overall, for the majority of people hospitalized, a burn represents a painful but temporary disruption of life's routine. After injury and treatment, they eventually resume normal preinjury functioning, which is largely independent of the burn area or location. However, for the subgroup of patients who have been found to experience long-term disruption in social, vocational, and physical functioning, services such as long-term psychotherapy, vocational counseling, and intensive outpatient physical rehabilitation are critical. The current direction in the field is focused on developing better screening tools to identify patients needing more intensive intervention earlier on, and more robust and widely available outpatient mental health services, particularly for patients in rural communities. ◗◗

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Multiple-Choice Questions

25. Which one of the following is a predictor of long-term adjustment to a burn injury?

    A. The etiology of the burn

    B. The size of the burn

    C. Premorbid level of functioning

    D. All of the above

26. Which one of the following would be appropriate pain control interventions for someone who is a repressor?

    A. Hypnosis

    B. Imagery

    C. Distraction

    D. All of the above

27. What issues should be addressed with patients during the resuscitative phase of recovery?

    A. Teaching appropriate coping strategies

    B. Examining the causes of the injury

    C. Listing the long-term consequences of the injury

    D. Protecting patients; natural defense mechanisms

28. Which one of the following statements is correct about pediatric burn injuries?

    A. Burn injuries should be regarded as a symptom rather than a cause of psychosocial problems in the family.

    B. Approximately 75% of pediatric burn patients come from dysfunctional families.

    C. More than half of children over the age of 4 with burn injuries have significant premorbid dysfunction.

    D. None of the above

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Best Practices in CME

Meeting the Psychosocial Needs of Burn Survivors and Their Families

By Shelley A. Wiechman, PhD

ID#: L003370

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

A patient's burn injury and his/her subsequent treatment is one of the most painful injuries one can experience. Treatment of most severe burns are managed by regional burn centers that have been accredited by the American Burn Association (ABA). Community providers need to be aware of the diverse needs of this population. The regional burn centers can be used as a resource for local health providers. This lesson focused on the emotional needs of burn survivors at each stage of recovery. It is critical that physicians caring for persons with burn injuries be aware of the emotional challenges patients may face as they provide comprehensive, patient-centered care. The current direction in the field focuses on better screening tools to identify patients needing early and intensive intervention, and robust and widely available outpatient mental health services, particularly for patients in rural communities.

Key Point 1: Burn Care is Multidisciplinary and Long term

Burn survivors face many challenges and the burn care team needs to include physicians, nurses, physical and occupational therapists, social workers, psychologists, vocational counselors, and nutritionist. Regional burn centers can be used as a resource for local providers upon discharge. Burn care starts in the ICU and continues across the life span as survivors often face unique physical and emotional issues related to their burn as they age.

Key Point 2: Emotional Needs Vary Depending Upon Their Stage of Recovery

Burn survivors and family members both face unique emotional challenges as they progress from the ICU, to the acute floor, to the outpatient rehabilitation setting, and then home. Addressing these emotional needs is crucial and supports the physical healing and demanding physical therapies and care.

Key Point 3: Nonpharmacological Management is Critical

Studies show that medications, such as opiates and benzodiazepines can only ameliorate some of the pain and anxiety that burn survivors face. Furthermore, these medications can have unwanted side effects. Nonpharmacological interventions for pain, anxiety, and sleep need to be implemented as an adjunct to medications. These nonpharmacological interventions need to be matched with a person's coping style.

Key Point 4: Recommendations

Early screening and intervention for pain, anxiety, and sleep is critical, with careful

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attention paid to those patients who have preinjury issues with depression, anxiety, and substance use disorders. In addition, the emotional needs of family members should be addressed. Appropriate interventions should be offered by the multidisciplinary treatment team and continued through the entire continuum of care.

Synthetic Cathinone and Cannabinoid Designer Drugs

Aviv Weinstein, PhD; Paola Rosca, MD, MPP; and Edythe D. London PhD

No commercial support was used in the development of this CME lesson.

KEYWORDS: Synthetic Drugs • Cathinone • Cannabis • Amphetamine • New Psychoactive Drugs

LEARNING OBJECTIVES: Clinicians will review recent evidence on the epidemiology, pharmacology, central nervous system effects, and other clinical findings and the regulation prevalence of synthetic drugs. They will be able to interpret the clinical findings and major symptoms and side effects of these drugs. Finally, readers will review the evidence on the potential abuse and dependence of these drugs.

LESSON ABSTRACT: As part of the increasing worldwide use of designer drugs, the recent use of compounds containing cathinones and synthetic cannabinoids has become particularly prevalent. This lesson reviews current literature on the prevalence, epidemiology, biobehavioral effects, and detection of these compounds amphetamine-type stimulants, including synthetic cathinones, and synthetic cannabinoids are widely used in Europe and the United States. Chronic use of synthetic cathinone compounds can have major effects on the nervous system and can induce paranoid psychosis and hypomanic illness with grandiose delusions, similar to the effects of other better-known amphetamine-type stimulants. Synthetic cannabinoid products have effects that are somewhat similar to those of natural cannabis. Some of these compounds are potent and dangerous, having been linked to psychosis, mania, and suicidal ideation. Novel compounds are developed rapidly, and new screening techniques are needed to detect them as well as rigorous reinforcement to prevent their distribution and use. Given the rapid increase in the use of synthetic cathinone and cannabinoid designer drugs, their potential for dependence and abuse and harmful medical and psychiatric effects, there is a need for research and education in the areas of prevention and treatment.

COMPETENCY AREAS: This lesson addresses the gap in learning in the areas of epidemiology, pharmacology, central nervous system effects, other clinical findings and regulation prevalence of synthetic drugs. Many clinicians lack an understanding of how to adequately identify the clinical symptoms of synthetic drugs and their harmful other medical and psychiatric medical symptoms. After reading this lesson, readers will have a better understanding of the use and consequences of synthetic drugs and how to diagnose and treat these new harmful and potentially dangerous addictive drugs.

Introduction

The past decade has witnessed a worldwide increase in the availability and use of novel psychoactive substances that produce "legal highs."[1-8] Usually mimicking the psychoactive effects of illicit drugs of abuse, these "designer" drugs vary widely in composition and are mainly sold online and from street retailers. Some of the drugs are advertised as being legal to sell, possess, and use; they are often labeled as "not for human consumption" to circumvent being subject to legislation. **Based on their pharmacological mechanisms and psychoactive properties, designer drugs fall into four major categories: amphetamine-like stimulants, which include cathinones derivatives and piperazine derivatives that are sold as substitutes for "ecstasy"; synthetic cannabinoids; hallucinogenic/dissociative agents; and opioid-like agents.[9]** As new compounds become available, information regarding their potential and the number of emergencies toxicity is scarce, related to their use is increasing.[10-11] Given the public health threat that is broad in scope and complexity, a multidisciplinary, coordinated effort is needed to elucidate the acute and long-term biological effects of synthetic drugs of abuse.[12]

This lesson focuses on synthetic cathinones and cannabinoid designer drugs. A recent global assessment of the appearance of new designer drugs shows that stimulants and synthetic cannabinoids constitute the top two categories of newly introduced psychoactive substances.[13] Synthetic cannabinoids show the greatest proliferation of new compounds, followed by phenethylamines and cathinones.

Synthetic Cathinones:

These drugs are psychostimulants related to the naturally occurring parent compound cathinone,[14-15] a psychoactive substance found in the khat plant (*Catha edulis*), which is a flowering plant native to the Horn of Africa and the Arabian Peninsula that has been chewed in these areas for thousands of years.

Khat contains a monoamine alkaloid called cathinone, an amphetamine-like stimulant, which is said to cause excitement, loss of appetite, and euphoria.

As members of the phenethylamine class of drugs, they are structurally and pharmacologically similar to amphetamine and *3,4-methylenedioxymethamphetamine*

(MDMA). The most commonly used drugs in this class have been *4-methylmethcathinone* (mephedrone), *3,4-methylenedioxy-N-methylcathinone* (methylone), and *4-methylenedioxypyrovalerone* (MDPV), although MDPV and mephedrone are no longer prevalent.[14-15] Reports of abuse of cathinone derivatives date back to the 1990s, when mephedrone was the first designer drug of this class.[16] Mephedrone is the most widely abused synthetic cathinone in Europe, and MDPV and methylone are the most frequently abused synthetic cathinones in the United States.[7] **These drugs have been commonly referred to as "bath salts," "plant food," or "fertilizer," because they were at times disguised and commonly included in products that were labeled and sold as such.[7, 9]**

New analogues, legal to possess, at least until they are formally banned, are frequently introduced, and it has been estimated that nearly 250 new analogues are produced each year.[17] These drugs are consumed by oral ingestion, inhalation, and snorting. Notably, the recent trend to supplement the use of more conventional psychostimulants, such as amphetamine and cocaine, with mephedrone, may lead to serious psychotic, neurological, cardiovascular, and sexual health consequences.[4]

Synthetic Cannabinoids:

Cannabinoid receptor agonists, which often mimic the effects of marijuana, are added to herbal mixtures that are mainly sold under different brand names, such as "Spice," in Europe since 2006.[18-19] According to *The United Nations Office on Drugs and Crime* (UNODC) 2015 report in 2014, synthetic cannabinoids account for the majority of *Novel Psychoactive Substances* (NPs) reported (39%).[9] These products are also called "K2," "herbal incense," "Cloud 9," "Mojo," and many other names.[20] Advertised as an "exotic incense blend that releases a rich aroma," "Spice" and "Spice-like preparations in Europe have been found to contain at least 9 new substances with various chemical structures, including those based on over 450 produced for medical research by John W. Huffman (e.g., JWH-018), HU-210 developed by Raphael Mechoulam at the Hebrew University, and the cyclohexylphenol ("CP") cannabinoids developed at Pfizer Pharmaceuticals.[21] AM-2201, an indole derivative that differs from JWH-018 by a fluorine atom in the pentyl chain, has nanomolar affinity at cannabinoid receptors[22] and is commonly

found in Korea. The emergence of synthetic cannabinoid drugs reflects the appearance of more than 100 known compounds that have cannabinoid receptor activity, and more are expected from new chemical structures with direct or indirect stimulation of CB1 cannabinoid receptors.

The perceived harmfulness of synthetic cannabinoids among secondary school students (12th grade) increased between 2012, the first year of measurement, and 2014, which may have contributed to the decline in use.[9] This review is divided into the following categories: epidemiology of use, pharmacology, neuropsychiatric findings, other medical conditions, and regulations.

Epidemiology

Synthetic Cathinones:

Recent surveys have considered the problem of synthetic cathinone use in the United States. In an online survey of 113 participants, who reported the use of synthetic cathinones, respondents were typically male, 18–24 years old, and Caucasian, with some college education.[23] Among them, past-year use was typically low (≤ 10 days), but marked by repeated dosing. The intranasal route of administration was the most frequent one reported, and subjective effects were similar to those of other stimulants (e.g., cocaine, amphetamines), the use of synthetic cathinones was associated with increased sexual desire and sexual risk behavior, and met *Diagnostic Manual of Mental Disorders, 5th Edition* (DSM-V) diagnostic criteria for a substance-related use disorder in more than half of the respondents. Self-reported prevalence of use of synthetic cathinones was less than that of marijuana, cocaine, *Salvia divinorum*, synthetic cannabinoids, methamphetamine, and MDMA. In another survey, reaching 2,349 students enrolled in 40 randomly selected courses at a large university in the Southeastern United States, 1.07% of the respondents endorsed ever using synthetic cathinones, and those who did were more often men than women, Hispanics and Native American rather than Caucasian students, and athletes more than non-athletes.[25]

Studies of synthetic cathinone use in Europe have also been informative. In Hungary, there has been a shift among street drug users from the use of heroin to mephedrone injection, potentially increasing the risk of severe psychiatric symptom profile and increased possibility of dependence.[24]

Among 1,006 individuals who completed a questionnaire survey in schools, colleges, and universities in Scotland (49.8% males 50% females), 20.3% reported previous use of mephedrone, with 23.4% reporting use on one occasion, and 4.4% endorsing daily use.[26] In a survey of 249 users of new psychoactive substances, interviewed in open public places, clubs, and discotheques in Slovenia, 67.9% of the respondents endorsed having tried either synthetic cathinones or amphetamines.[27] Of those who reported using synthetic cathinones or amphetamines, most reported having used 3-methylmethcathinone first, 43.0% had first tried methylone, and 37.3% had first tried mephedrone. Users attributed high risks to the new drugs and preferred traditional drugs.

A report on the occurrence and trends of new synthetic drugs in Sweden included participants who were 13–63 (median 20) years of age.[28] The report documented a widespread use of many different synthetic drugs mainly by adolescent and young male (79%) adults, among cases of drug intoxications presenting at emergency departments and intensive care units across the country. Of the initial 189 blood and urine samples submitted for laboratory investigation, 156 (83%) tested positive for at least one drug. More than 50 new synthetic drugs were detected. These included synthetic cannabinoid receptor agonists ("Spice"), piperazines, substituted phenethylamines, synthetic cathinones, hallucinogenic tryptamines, piperidines, opioid-related substances, ketamine and related substances, and γ-aminobutiric acid (GABA) analogues. About half of the cases involved multiple drug intoxications, making it hard to link the clinical presentations with one specific substance.

Synthetic Cannabinoids:

Synthetic cannabinoid users are usually men in their twenties, who also use other drugs. In a study of adult marijuana and tobacco users, the 42 respondents were primarily young adults, male, racially diverse, high school graduates, and nearly all currently smoked tobacco and cannabis, with 86% smoking cannabis on five or more days per week.[29] Nearly all (91%) were familiar with synthetic cannabinoid products, half (50%) reported smoking them previously, and a substantial minority (24%) reported use in the month before the survey.

Common reasons reported for use included, seeking a new "high" similar to that produced by marijuana, while avoiding detection of drug use via urine toxicology. The primary side effects were trouble thinking clearly, headache, dry mouth, and anxiety. Students also reported using synthetic cannabinoids for curiosity, to get high, and the fun of feeling high.[30] Eleven adolescents described a feeling of euphoria and memory changes, and 9 of them reported negative mood changes.[31]

Several informative surveys of synthetic cannabinoid use have involved college students. In a study of 852 college students in the United States, 69 (8%) reported using the drugs at least once, and use was more common in males than female respondents and in first- or second-year college students than third-year students.[32] A survey of students recruited from a local health clinic and a U.S. university at the U.S./Mexico border found 9%, 5%, and 3% lifetime, past-year, and past 30-day use of synthetic cannabinoids, respectively.[33] In Rhode Island, of 1,080 young individuals (18–25 years old) surveyed between January 2012 and July 2013, 9% reported use of synthetic cannabinoids in the last month. Synthetic cannabinoid use was associated with male gender, not going to school, and with the use of cigarettes, binge alcohol drinking, daily and weekly marijuana use, and other drug abuse.[34] A survey of 3,146 students at 11 colleges in North Carolina and Virginia showed that the lifetime prevalence of synthetic cannabinoids at college entry was 7.6%.[35] An additional 6.6% of students reported first use during college. By the cohort's fourth year, 17.0% reported lifetime synthetic cannabinoid use.

A nationally representative sample of high school seniors in the Monitoring the Future study between 2011 and 2013 included 11,863 participants of mean age 18.[36] Ten percent reported no recent use and 3% reported frequent use ≥ 6 times) of synthetic cannabinoids. Females were at low odds for use, and going out 4–7 evenings per week for fun consistently increased the odds of use. **Lifetime use of alcohol, cigarettes, and other illicit drugs all robustly increased the odds for synthetic cannabinoid use, but the frequency of lifetime marijuana use was the strongest correlate with more frequent use, further increasing the odds of synthetic cannabinoid use.**

Among 396 patients entering residential treatment for any substance use disorder in the United States, 150 reported using synthetic cannabinoids in their lifetimes. Motives for drug use included curiosity (91%), feeling good/getting high (89%), relaxation (71%), and getting high without having a positive drug test (71%).[37]

In an anonymous online survey among 14,966 participants in the UK, 2,513 (17%) reported the use of synthetic cannabinoids. Among them, 41% reported their use in the last 12 months.[38] Almost all recent synthetic cannabinoids users (99%) reported having used natural cannabis at least once. Synthetic cannabinoids reportedly had both a shorter duration of action and faster time to peak onset of effect than natural cannabis. Natural cannabis was preferred to synthetic cannabinoids by 93% of users, with natural cannabis rated as having greater pleasurable effects when high and allowing better function after use. Synthetic cannabinoids were associated with negative effects, hangover effects, and greater paranoia. In an anonymous follow-up online survey of drug use with 22,289 respondents, the relative perceived risk associated with the use of synthetic cannabinoids was estimated as 30 times higher than that associated with natural cannabis.[39]

In Australia, a sample of 316 synthetic cannabinoid users (77% male, mean age 27 years) reported a mean duration of synthetic cannabinoid use of 6 months, 35% reported weekly use or more often, and 7% reported daily use.[40] Reasons for first use included curiosity (50%), legality (39%), availability (23%), recreational effects (20%), therapeutic effects (9%), non-detection in standard drug screening assays (8%), and aid for the reduction or cessation of cannabis use. In a further study of 1,126 students (mean age 14.9 years) from 11 secondary schools in Australia, 2.4% had ever used synthetic cannabis, and 0.4% had used synthetic stimulants.[41] Users were more likely to have had an episode of binge drinking in the past 6 months, tried tobacco and had higher levels of psychological distress and lower perceived self-efficacy to resist peer pressure than non-users, but did not significantly differ from users of other illicit drugs.

Comparative Epidemiology:

In a survey covering the years 2009 to 2012 in the United States, synthetic cathinone and synthetic cannabis exposures totaled 7,467 and 11,561, respectively,[42] with

increases in the use of both from 2009 to 2011. Synthetic cathinone use increased from none reported in 2009, to 298 in 2010, and 6,062 in 2011. By comparison, there were 14 reported synthetic cannabis exposures in 2009, 2,821 in 2010, and 6,255 in 2011. First-time synthetic cathinone exposures were lower in 2012 (n = 1007) than in 2011 (n= 2027) and synthetic cannabis exposures were higher in 2012 (n = 2389) than in 2011 (n = 1888), possibly reflecting a shift from synthetic cathinone use towards the use of synthetic cannabinoids. Most exposures occurred in the Midwest and Southeastern U.S. (64.8% of synthetic cathinone and 58% of synthetic cannabis exposures). Males comprised 69% (n = 5153) of synthetic cathinone users and 74% (n = 8505) of synthetic cannabis users. Use of synthetic cathinones was highest in individuals 20–29 years of age (n = 2943), and the use of synthetic cannabinoids was highest for younger respondents, i.e., individuals 13–19 years of age (n = 5349). In conclusion, synthetic cannabis emerged first with overall more reported exposures than synthetic cathinone. In 2012, synthetic cathinone abuse declined while synthetic cannabis abuse increased. Young men intentionally abusing synthetic cannabinoids via inhalation make up the majority of users.

Pharmacology, CNS Effects, and Other Clinical Findings

Synthetic Cathinones:

Similar to the action of other psychomotor stimulants, synthetic cathinones target plasma membrane transporters of the monoamine neurotransmitters, dopamine, norepinephrine, and serotonin,[43] Mephedrone and methylone act as nonselective transporter substrates, thereby promoting non-exocytotic release of all of these neurotransmitters, but MDPV does not act as a transporter substrate. MDPV acts as a potent blocker at catecholamine transporters with little effect at the serotonin transporter.[43]

The administration of mephedrone or methylone to rats increases extracellular concentrations of dopamine and serotonin in the brain, analogous to the effects of MDMA.[43] Not surprisingly, synthetic cathinones elicit locomotor stimulation in rodents. The enhancement of dopamine transmission by synthetic cathinones predicts

a high potential for addiction and may underlie adverse effects.[44] See Appendix A for behavioral and pharmacological findings regarding the effects of synthetic cathinones in rodents.

Low doses of synthetic cathinones acutely produce euphoria and increase alertness, but high doses or chronic use can cause serious adverse effects, such as hallucinations, delirium, hyperthermia, and tachycardia.[57] Repeated use of synthetic cathinones is associated with paranoid hallucinatory delirium. Some patients who use these substances develop a syndrome, termed, "excited delirium," of extreme agitation and violent behavior after using other stimulant drugs, such as amphetamines.[57] These patients frequently exhibit dehydration, skeletal muscle damage, and renal failure that may lead to multi-organ failure and death. An exemplary case of "excited delirium" after ingesting "bath salts" is that of a 40-year-old male, who had no past psychiatric history and presented with psychosis and violence after taking this substance.[58] Forty-three post-mortem cases with detected synthetic cathinones had the following associated causes of death: driving under the influence (17 cases): 2 domestic violence, 4 suicides, 12 overdoses, 6 accidents, 1 drug-facilitated assault, and 1 homicide.[59] A case of suicide by hanging had the highest measured MDPV concentration, and a driver had the highest methylone concentration. A single case of death following methylone ingestion was reported in France.[60]

The most frequent medical complications of synthetic cathinone use are cardiovascular effects (e.g., tachycardia, hypertension) and hallucinations. Among cases reported to Texas poison centers during 2011-2010, the most frequently reported unwanted clinical effects were tachycardia (45.9%), agitation (39.2%), hypertension (21.0%), hallucinations (17.7%), and confusion (13.0%).[61] A retrospective study of "bath-salt" exposure, reported to two poison centers in the United States, found that clinical effects were primarily neurological and cardiovascular. These included agitation (n = 194), combative behavior (n = 134), tachycardia (n = 132), hallucinations (n = 94), paranoia (n =86), confusion (n = 83), chest pain (n = 40), myoclonus (n = 45), hypertension (n= 41), mydriasis (n = 31), elevations in creatine phosphokinase (n = 22), hypokalemia (n = 10), blurred vision (n = 7), and death (n = 1).[62] Signs of severe

toxicity, consistent with excessive serotonin activity, such as hyperthermia, metabolic acidosis, and prolonged rhabdomyolysis, were also reported.[63]

A single case described cardiovascular manifestations, including tachycardia, hypertension, myocardial infarction, arrhythmias, and cardiac arrest.[64] Synthetic cathinone exposure has also resulted in many cases of seizures in the pediatric population. The American Association of Poison Control Centers database was used to identify all known synthetic cathinone exposures in children and youth <20 years of age between 2010 and 2013.[65] There were 1,328 pediatric synthetic cathinone exposures where seizures complicated 73 (5.5%) of the cases, with 37 (50.7%) involving a single seizure, 29 (39.7%) multiple seizures, and seven (9.6%) status epilepticus. Fever and acidosis were associated with single seizures, multiple seizures, and status epilepticus. There were no correlations between any seizure activity and electrolyte abnormalities, hallucinations and/or delusions, tachycardia, or hypertension. Co-ingested substances were present in 33 (45%) of seizure cases, the most commonly used were tetrahydrocannabinol, alcohol, and opioids. Finally, in Italy, a case of a neonatal withdrawal syndrome in a baby born to a woman who was a chronic consumer of 4-methylethcathinone was documented. The newborn presented with increased jitteriness and irritability, high-pitched crying, hypertonia in the limbs and brisk tendon reflexes.[66]

Synthetic Cannabinoids

Unlike *D9-tetrahydrocannabinol* (THC), synthetic cannabinoids are high-potency, high-efficacy, full agonists at cannabinoid receptors,[67-68] including CB1 receptors in the brain,[69-74] There is substantial variability in the molecular constituents of different products, between batches of the same product, and even within a package.[18] In addition to synthetic cannabinoids, Spice has been reported to contain preservatives, additives, fatty acids, amides, esters, the benzodiazepine phenazepam, and O-desmethyltramadol, an active metabolite of the opioid medication tramadol.[75-77]

Studies in rodents have indicated that most synthetic cannabinoids produce effects and toxicity that, overall, are similar to those of THC. These include hypothermia, analgesia, hypo-locomotion, and akinesia. Specifically,

JWH-018 administration inhibits sensorimotor responses at lower doses, reduces spontaneous locomotion at intermediate/high doses, and induces convulsions, myoclonia, and hyperreflexia at high doses.[84] Other studies showed reduced locomotor activity and depressant effects,[85] locomotor suppression, antinociception, hypothermia, and catalepsy.[86] JWH-18 impairs motor activity and induces catalepsy in mice, and the effects are more severe than those of Δ(9)-THC.[88]

Cannabis use has the potential for inducing psychosis (see recent reviews 92-94), and it would be reasonable to expect synthetic cannabinoids to have the same effect. Because of their high potency and the fact that synthetic cannabinoids act as full cannabinoid receptor agonists, even short or occasional use of the synthetic compounds can produce untoward effects, such as insomnia, memory impairment, headaches, dizziness, and delusions.[92] Moreover, in contrast to natural cannabis, synthetic cannabinoid preparations contain no cannabidiol, which may be protective against psychosis. Cannabidiol antagonizes the psychotomimetic and other psychotropic effects of THC, although the mechanisms responsible for its therapeutic potential are still not clear.[95] These drugs, therefore, may have a higher psychosis-inducing potential than cannabis. Compared with natural cannabis, synthetic cannabinoids may cause more frequent and more severe unwanted negative effects, especially in young users. **Case reports have documented psychosis,[96-98] mania[99] and suicidal ideations[100] in synthetic cannabinoid users.**

Although brain imaging has pointed to abnormalities in cerebral perfusion, deficits in brain volume as well as in white-matter pathways,[101] brain imaging has scarcely been applied to understand the neural correlates of synthetic cannabis use. A comparison of 20 male patients who had used synthetic cannabinoids with 20 healthy male controls indicated that the drug users had smaller grey-matter volume in both the left and right thalamus and the left cerebellum,[102] with no correlation between the age of first cannabis use, duration of use, frequency of use, and total grey-matter volume. In a case report, a 23-year old patient experiencing a severe withdrawal syndrome upon voluntary abstinence from "Spice Gold" reported craving, affective symptoms, and a range of somatic complaints, which resolved after

several days of monitored abstinence.[103] Dopamine D2/3 receptor availability was 20% lower in the striatum and in extra-striatal regions compared to values in healthy control participants, but returned to control values with detoxification. These reports suggest that synthetic cannabinoid use can produce remarkable changes in the brain, but the studies are preliminary, and the extent and duration of the neural sequelae of synthetic cannabinoid use is still unknown.

Reports concerning driving under the influence of synthetic cannabinoids also reflect their impact on the nervous system. One report from the United States indicated that drivers under the influence of synthetic cannabinoids had slow and slurred speech, and that coordination was poor.[128] A survey in Germany found behavioral deficits that were moderate, except for aggravation of paranoia in one case.[129] The symptoms were either compatible with the effects of cannabinoid agonists or attributable to alcohol or other drugs found in the blood samples. In several case reports, sedating effects and impaired fine motor skills were noted.[126] In Poland, a single case showed that the drug produced effects and impairment similar to THC.[130] Very few cases of synthetic cannabinoids were detected in the blood of drivers in Norway.[131-132]

Synthetic cannabinoid use has been associated with serious adverse health effects on multiple systems, and with death.[104-106] For example, among 3,572 calls related to synthetic cannabinoid use to call centers in the United States, 2,961 had a medical outcome, 11.3% of callers had a major adverse effect, and 15 deaths were reported.[107] The most commonly reported side effects are tachycardia, agitation, irritability, confusion, dizziness, drowsiness, hallucinations, delusions, hypertension, nausea, vomiting, vertigo, and chest pain.[20, 56, 107-108] Central nervous system effects covered the range from headache to coma, and included seizures, myoclonus, catatonic stupor, cerebral ischemia, and encephalopathy.[104, 109, 110-112] Case reports have documented cardiac complications, ranging from chest pain.[113] to myocardial infarction,[114-115] and cardiac arrest.[116-118] Cases of acute kidney damage and renal failure, following the use of synthetic cannabinoids, have also been reported.[119] Dyspnea, rhabdomyolysis, diaphoresis, and hypokalemia, which are not commonly reported with cannabis use,

have been associated with synthetic cannabinoid use as well.[20, 105] Case reports have also mentioned respiratory depression[120] and, with chronic use of synthetic cannabis, pulmonary complications and pneumonia.[121-122] Rare cases of Cannabinoid Hyperemesis Syndrome were described, which were characterized by cyclical nausea and vomiting, abdominal pain, and an unusual compulsion to take hot showers.[123-124]

A withdrawal syndrome from prolonged habitual use of synthetic cannabinoids has been reported both in case reports and a study of 47 patients admitted to detoxification services.[125, 126] The symptoms were similar to those of withdrawal from THC, including anxiety, myalgia, chills, anorexia, mood swings, and tachycardia, but were more severe and did not seem to improve with the administration of THC.[125, 127] The differences in presentation may reflect the inclusion of extraneous compounds, including amphetamine-like substances.

Regulation and Legislation

Responding to the rapid appearance of novel psycho-active substances with molecular structures that have not been covered by legislation, the governments of several countries have recognized the need for new mechanisms of control with accelerated ways to curtail the free sale and distribution of these substances.[133] In Europe, since 1997, three levels of control have been introduced: Early Warning System, risk assessments of newly emerged substances (performed by the European Monitoring Centre for Drugs and Drug Addiction scientific committee), and European Council decisions advocating new legislations.[134] The possession, use, and synthesis of synthetic cathinones became subject to legal classification in Europe in 2010,[134] and in the United States in 2011.[135] Some countries, such as Denmark, the UK, and Israel,[136] opted for "temporary bans" of new psycho-active substances considered to pose a danger to public health during which a risk assessment of a particular compound could be performed thus facilitating its subsequent inclusion into the Dangerous Drugs Ordinance. Other countries, such as New Zealand,[137] Ireland, Poland, and Romania,[138] chose a "pre-market approval" regulation regime for synthetic drugs that pose a low health risk on the basis of pre-clinical and clinical evidence. The effectiveness of these innovative

legal measures and regulations on the selling and marketing of the new psychoactive substances still needs to be assessed.

Summary

Exposure to and the use of synthetic cathinones and synthetic cannabinoids are becoming increasingly popular, despite the potential harms of these substances. Synthetic cathinones have similar clinical effects to amphetamines and MDMA, whereas synthetic cannabinoids are high-potency, full agonists at cannabinoid receptors. Both classes of substances have adverse health effects. Synthetic cathinones cause anxiety, agitation, panic, dysphoria, psychosis, and bizarre behavior whereas synthetic cannabinoids cause agitation, irritability, confusion, hallucinations, delusions, psychosis, and death (as well as other health problems noted above).

The chronic use of synthetic cannabinoids and synthetic cathinones results in adverse medical and psychiatric effects that seem to be higher than that of natural cannabinoids. Synthetic cannabinoids and synthetic cathinones also show high toxicity compared with natural cannabinoids. In comparison with other known amphetamines, synthetic cathinones such as MEPH and MDPV exhibit a pharmacological profile that is more typical of methamphetamine and cocaine, respectively, while methylone shows a pharmacological profile that more closely resembles MDMA, but the clinical toxicology of synthetic cathinones is poorly characterized. In view of the increasing popular demand for these substances and their grave dangers, there is an urgent need for more rigorous research on the effects of synthetic cathinones and synthetic cannabinoids to help clinicians manage adverse events and to better understand their pharmacological effects on humans. ⬗

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Multiple-Choice Questions

29. The major types of synthetic drugs are believed to be those described below, *except*:

A. amphetamine-like stimulants.

B. synthetic cannabinoids.

C. hallucinogenic agents.

D. sedatives.

30. Which of the following statements are reasons people use synthetic cannabinoids?

A. Getting "high"

B. Avoiding detection

C. Enhancing sexual experiences

D. All the answers are correct

31. According to the lesson, which of the following are believed to be possible symptoms of synthetic cannabis?

A. Obsessive-compulsive behavior

B. Suicidal ideation

C. Psychosis

D. All the answers are correct

32. According to the lesson, all of the following are believed to be common symptoms of synthetic cathinones, *except*:

A. blurred vision.

B. hallucinations.

C. agitation.

D. cardiovascular effects.

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Best Practices in CME

Synthetic Cathinone and Cannabinoid Designer Drugs

By Aviv Weinstein, PhD; Paola Rosca, MD, MPP; and Edythe D. London PhD

ID#: L003371

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

This lesson reviews how novel psychoactive substances affect physical and mental health and how these substances challenge what we know about drugs of abuse. Novel psychoactive substances are highly popular and very difficult to detect hence they pose a variety of psychological and legal challenges to our public health system. They are responsible to the development and course of mental disorders especially psychotic episodes and also predisposition to chronic mental illness and cognitive deficits. The negative impact of psychoactive substances on mental health and function demands careful assessment and detection by legal and psychiatric practice.

Key Point 1: Prevalence of Novel Psychoactive Substances

Epidemiologic surveys reveal that in the general population the median prevalence rate for synthetic cannabinoids in Europe is about 8% and of synthetic cathinones stands lower at 4.4%. There are differences between these rates in Europe and the US and among groups of youth drug users in Europe prevalence is much higher and can rise to 66%.

Key Point 2: Assessment

Evidence shows that consumers of novel psychoactive substances have severe, persistent, and recurring mental disorders such as psychosis, mania, and major depression as well as insomnia, memory impairment, headaches, dizziness, delusions and obsessive-compulsive symptoms. Therefore a thorough assessment of the use of these substances in every single patient as early as possible in the clinical evaluation process is a key to identify the symptoms in order to provide adequate treatment of co-occurring psychiatric disorders.

Key Point 3: Prognosis

Studies show that persons who use novel psychoactive substances are at highly increased risk for the development of subsequent mental disorders and other psychological difficulties. As a consequence, these at-risk patients should be observed and followed carefully once they have entered the health care system.

Key Point 4: Recommendations

Clinicians should adopt routine assessment of their patients' drug use patterns as early as possible in the clinical process and incorporate this important information in their treatment decisions. Although the assessment of novel psychoactive substances poses a challenge to psychiatric practice because there are difficulties in detecting such substances and assessment methods have their limitations, an appropriate assessment procedure is the most accurate method for both the assessment and treatment of novel psychoactive substances.

Notes

Closing the Treatment Gap for Mental, Neurological and Substance Use Disorders by Strengthening Existing Health Care Platforms: Strategies for Delivery and Integration of Evidence-based Interventions

Rahul Shidhaye, MBBS, MD; Crick Lund, BA, BSocSci, MA, MSocSci, PhD; and Dan Chisholm, PhD

LEARNING OBJECTIVES: Clinicians will review a framework of integrated collaborative care using the World Health Organization's pyramid of self-care, primary care, and specialist care. Readers will review a set of evidence-based interventions and strategies to implement these principles into practice.

LESSON ABSTRACT: This paper outlines the main elements and features of a mental health care delivery platform and its delivery channels. These include evidence-based interventions that can be delivered via this platform as well as broader health system strengthening strategies for more effective and efficient delivery of services. The focus is broadly on health systems perspective rather than strictly disorder-oriented intervention analysis. A set of evidence-based interventions within the WHO pyramid framework of self-care, primary care, and specialist care have been identified; the main challenge lies in the translation of that evidence into practice. The delivery of these interventions requires an approach that puts into practice key principles of public health, adopts systems thinking, promotes whole-of-government involvement and is focused on quality improvement. Key strategies for effective translation of evidence into action include collaborative stepped care, strengthening human resources, and integrating mental health into general health care. In order to pursue these principles and strategies using a platform-wide approach, policy makers need to engage with a wide range of stakeholders and make use of the best available evidence in a transparent manner.

COMPETENCY AREAS: This lesson addresses the gaps in learning in the areas of: working in interdisciplinary teams, patient care, and employing evidence-based practice and applying quality improvement. Readers will gain knowledge of how to integrate self-care, primary care, and specialist care in a collaborative platform and review strategies to deliver evidence-based interventions into practice.

Background

A large proportion of persons affected by *mental, neurological and substance use* (MNS) disorders do not have access to a wide variety of evidence-based interventions which can prevent and treat these disorders, resulting in a huge treatment gap.[1] This problem is not just limited to MNS disorders as cost-effective interventions in other health sectors are inadequately provided and underused.[2] De Savigny and Adams have mentioned, "evidence-based interventions often fail to achieve their goal, not so much due to the inherent flaw in the interventions themselves, but due to the unpredictable behavior of the system around them."[2] Multiple barriers related to human resources, infrastructure, information and service provision, people's participation, knowledge, perception of services, help-seeking behavior and overall stewardship and governance related issues affect health system performance.[2] As the effectiveness of MNS disorders is largely determined by the health systems in which they are nested, it is essential to shift focus from a strictly disorder-oriented or 'vertical' perspective to a more health systems strengthening or 'horizontal' approach. There is also a strong evidence-base supporting common environmental risk factors (such as unhealthy lifestyles) leading to mental and physical non-communicable diseases, often presenting as co-morbidities and treatments for one condition may have side effects that increase the risk of another condition.[3] There are several other reasons for integrating MNS care into general health care systems, including the limited number of specialist healthcare providers, reduced mental health stigma from receiving care in general healthcare services and improved efficiencies.

In the real-world setting, implementation of evidence-based interventions for MNS disorders seldom occurs through the delivery of single vertical interventions, rather these interventions are delivered via so-called platforms—the level of the health or welfare system at which interventions or packages can be most appropriately, effectively, and efficiently delivered.[4]

This paper seeks to identify evidence-based interventions that can be appropriately packaged for one or more specific MNS disorders, as well as for different levels or platforms of the health or welfare system. A particular platform is defined based on WHERE the intervention

will be delivered (the setting) and WHO will deliver the intervention (the service provider). A specific delivery channel such as a school or a primary health care centre represents the vehicle for the delivery of a particular intervention on a specified platform. Identifying the set of interventions that fall within a particular platform or delivery channel will help decision makers to identify potential opportunities, synergies, and efficiencies. In addition, it is to these delivery platforms or channels that resources are often allocated in practice, for example, to schools or primary health care services, rather than to specific interventions or disorders.

In this paper we outline the main elements and features of a MNS care delivery platform and its delivery channels, such as self-care informal health care, primary health care, or specialized services. We consider evidence-based interventions that can be delivered in general health care settings and MNS care settings, as well as broader health system strengthening strategies for more effective and efficient delivery of services on this platform.

Evidence-based interventions that can also be delivered via population or community platforms—ranging from legislative and regulatory measures aimed at restricting access to means of self-harm/suicide and reducing demand for alcohol to parenting programs during infancy or socio-emotional learning programs for vulnerable—have also been identified and are reported elsewhere.[5]

Elements of a Mental Health Care Delivery Platform

Health care services as a delivery platform for improving population mental health comprise three interlinked service delivery channels: self-care and informal health care; primary health care; and specialist health care. These three key delivery channels map well onto the commonly cited *Service Organization Pyramid for an Optimal Mix of Services for Mental Health* by the World Health Organization (WHO)[6] (Fig. 1).

At each subsequent level of the pyramid the mental health needs of individuals become greater and require more intensive professional assistance, usually resulting in higher costs of care.

Table 1:
Pyramid for an Optimal Mix of Services for Mental Health

World Health Organization service organization pyramid for an optimal mix of mental health services.
Source: [Organization of Services for Mental Health: Mental Health Policy and Service Guidance Package. Geneva: WHO, 2003.]

Self-care and Informal Health Care:

The foundation of the health care delivery platform rests on self-care and emphasizes health worker–patient partnerships. Persons with MNS disorders and psychosocial disabilities, and their family and friends, play a central role in the management of the mental health problems. The role of individuals may range from collaborative decision-making concerning their treatment, to actively adhering to prescribed medication, to changing health-related behaviors, such as drug and alcohol use, self-management of stress and identification of seizure triggers. Informal health care comprises service providers who are not part of the formal health care system, such as traditional healers, village elders, faith-based organizations, peers, user and family associations, and lay people.[6] Traditional healers are of particular significance as populations throughout East Asia and Pacific, South Asia, Latin America and the Caribbean, and Sub-Saharan

Africa often use traditional medicine to meet their health needs.[7] Peers are a key human resource at this level of health care. Peer-led education and behavioral interventions have been effective for a number of target populations with health issues in LMICs.[8, 9, 10] Mental health self-help groups form another key component of informal community care. Mental health self-help groups may be defined as, "any mutual support oriented initiative directed by people with MNS disorders or their family members."[11] However, informal community care should not be viewed as a substitute for publicly funded, evidence-based mental health care. One of the proximal determinants of help seeking by individuals is the perceived need for care which in turn is dependent on various socio-cultural factors as well as knowledge, attitudes and values that people have towards the health care system.[12] 'Mental health literacy' refers to people's knowledge and beliefs about MNS disorders which aid their recognition, management and help seeking choices. Effective awareness-raising campaigns can result in increased presentation of persons with mental health disorders to primary health care and improved service utilization.[13] In addition to this it is important to develop locally valid ways of understanding, communicating and augmenting perceived needs of people especially with common mental disorders and substance abuse as it has been observed that primary care services have difficulty in identifying and engaging patients with these disorders compared to severe mental disorders. It is also important for clinicians to develop their understanding of local idioms of distress, in order to provide culturally appropriate care.

Primary Health Care:

Delivery of services for MNS disorders through primary health care is a fundamental component of a health care delivery platform, since it serves as the first level of care within the formal health care system. The strong emphasis on primary health care is due to the fact that the services provided at this level of the health system are generally accessible, affordable, and acceptable for individuals, families, and communities.[6] Where the provision of mental health care is integrated into these services, access is improved, MNS disorders are more likely to be identified and treated, and

comorbid physical and mental health problems can be managed more seamlessly.

Specialist Health Care:

Psychiatric Services in General Hospitals and Community Mental Health Services

People with severe MNS disorders may require hospitalization at some point. First-level hospitals (typically at the district level) provide an accessible and acceptable location for 24-h medical care for people with acute worsening of disorders, in the same way that these facilities manage acute exacerbations of physical health conditions.[6]

In addition, there is a need for specialist mental health services in the community for severe cases that cannot be managed by generalists. Examples include assertive community treatment teams and community outreach teams, which provide support to service users to enable them to continue to function in the community without requiring admission, and close liaison with general primary care services and other social and criminal justice services.[6]

Extended-stay Facilities and Specialist Psychiatric Services

A small minority of people with MNS disorders will require specialist care beyond that provided in first-level hospitals.[6] For example, people with treatment-resistant or complex presentations may need to be referred to specialized centers for further testing and treatment. Others may occasionally require ongoing care in community-based residential facilities due to their severe mental disorders or intellectual disabilities and lack of family support. **Forensic psychiatry is another type of specialist service in this category.** The need for referral to specialist and extended-stay services is reduced when general hospitals are staffed with highly specialized health workers, such as psychiatrists and psychologists.

Relationships Between Different Delivery Channels

No single service delivery channel can meet all mental health needs. For example, primary mental health care must, on the one hand, be complemented by specialist care services to whom primary health workers **can turn for referrals, support, and supervision;** on the other hand, primary mental health care needs to promote and support self-care and informal community care that encourages the involvement of people in their own recovery. Support of self-care and management can be provided via routine primary care visits or via group sessions led by health or lay workers in health care settings or community venues. In short, the potential of the health care system as a delivery platform for enhanced mental health and well-being can only be fully realized if genuine continuity and collaboration of care occur across the three service delivery channels; the continuity and collaboration, in turn, rely on an appropriate flow of support, supervision, information-sharing and education.

Evidence-based Interventions for Health Care Delivery Platforms

A strong evidence base supports integrated services across the different delivery channels of the health care platform. This evidence has been synthesized in a number of publications, including the *mhGAP Intervention Guide,*[14] a series of papers on packages of care for MNS disorders in LMIC, published in *PLoS Medicine,*[15] and a WHO-WONCA report on mental health in primary health care.[16]

For each of the delivery channels, interventions may be categorized as follows:

- **Promotion and primary prevention**

- **Identification and case detection**

- **Treatment, care, and rehabilitation.**

System Strengthening Strategies for Integrated Health Care Delivery

The availability of evidence-based interventions does not ensure their translation into practice. It is critical to address the question of how to integrate evidence-based mental health care interventions into primary care and self-care delivery channels and how to link this integration to specialist care. A comprehensive and multifaceted approach that contains the following elements is essential

Table 1:

Examples of Evidence-Based Interventions Relating to The Health Care Delivery Platform by Various Delivery Channels

Delivery channel	Promotion and primary prevention	Identification and case detection	Treatment, care, and rehabilitation
Self-care and informal health care	Adoption of a healthy lifestyle, including diet and physical activity relaxation training Self-monitoring of high risk behaviors, such as substance abuse	Self-detection of depression and anxiety disorders	Web-based psychological therapy for depression and anxiety disorders Self-managed treatment of migraine Self-identification and management of seizure triggers Improving adherence to anti-epileptic treatment by intensive reminders and implementation intention interventions
Primary health care	Parent skills training for internalizing and externalizing problems in child and parental mental health	Screening for developmental delays in children Screening and brief interventions for alcohol use disorders by trained primary health care staff Community-based case finding of psychosis and severe depression Diagnosis of depression, anxiety disorders, maternal depression, alcohol use disorders, dementia, headaches, and epilepsy	Management—pharmacological and psychosocial interventions—of depression, anxiety, psychosis, bipolar disorder, alcohol use disorders, epilepsy, dementia, and drug use based on mhGAP Intervention Guidelines Psychological treatment for depression, anxiety, ADHD, disruptive behaviour disorders in children Cognitive behavioral therapy-based interventions for depression and anxiety disorders in adults and mothers in perinatal period Management of alcohol withdrawal in conjunction with motivational interviewing and motivation enhancement involving family and friends Interventions for caregivers of patients with psychosis and dementia Improve quality of antenatal and perinatal care to reduce risk factors associated with intellectual disability Primary healthcare packages for underlying MNS disorders (for suicide and self-harm) Planned follow-up and monitoring of suicide attempters Emergency management of poisoning
Specialist health care		Diagnosis of complex childhood mental disorders Diagnosis of severe psychosis and depression Diagnosis of secondary causes of headache Screening of new-born babies for modifiable risk factors for intellectual disability	Electroconvulsive therapy for severe refractory depression Surgical interventions for refractory epilepsy Pharmacological management of dementia (cholinesterase inhibitors and memantine) Methadone maintenance therapy for opioid dependence, buprenorphine as opioid substitution therapy Management of refractory psychosis using clozapine Management of severe alcohol dependence (along with withdrawal) Management of severe maternal depression using antidepressants Stimulant medication for severe cases of attention deficit hyperactivity disorder Cognitive behavioral therapy based interventions and anger control training for adolescents with disruptive behavioral disorders

for the successful integration of mental health into health care systems:

- A *whole-of government approach* involves the promotion, pursuit, and protection of health through concerted action by many sectors of government. These include ministries of planning and development, finance, law and justice, labor, education, and social welfare. The health system cannot tackle the health, social, and economic determinants and consequences of MNS disorders alone.

- A *public health approach* stresses the establishment of partnerships between patient and service providers, as well as equitable access for the whole population.[17] This approach requires the integration of care at the patient level. Services should be person-centered and coordinated across diseases and settings. Collaborative, coordinated, and continuing care, within a framework of evidence-based interventions, provides the foundation of the public health approach. This means providing good-quality, accessible services to those in need, as well as preventing the onset of disease and promoting mental health and well-being over the entire life course.[18]

- A *systems approach* to integrated service planning and development encompasses the critical ingredients of a health system—good governance, appropriate resourcing, timely information, as well as the actual delivery of health services or technologies—that need to be in place for desired health outcomes or program goals to be realized. Effective governance, strong leadership, and cogent policy-making merit particular mention, since they provide the framework for appropriate action and subsequent service development. Indeed, a well-articulated mental health policy, along with a clear mental health implementation plan and budget, is a strong driver for change and can appreciably boost efforts to deliver mental health services at primary care level.[16]

It is also imperative to understand that 'context' in the form of local health system and social influences are inextricably tied up with the outcomes of service delivery changes. Literature from high-income countries suggests that the interventions that work in initial studies lose their effectiveness as they are implemented widely.[19] The effectiveness of an intervention is often based on studies in a small number of settings and the full range of complexity of the intervention may not be fully understood, ultimately resulting in the intervention working in only 50% of replication sites, implying an equal chance that it will or will not work.[20] Many health systems lack the capacity to integrate new evidence-based interventions and when such systems are not well understood, even the simplest intervention can fail.[2] Nested within the wider health systems strengthening approach, we describe a number of specific strategies for integrated mental health care delivery, but is should be borne that they are context-specific and may not be generalizable in all settings. Nevertheless, the learnings from the relevant literature can be applied after suitable contextual adaptation.

Strategy 1. Improving the Organization and Delivery of Services through Collaborative Stepped Care:

Collaborative care **is an evidence-based approach to improve the management of MNS disorders at the primary care level. The overall aim of collaborative care is to enhance the quality of care and quality of life, consumer satisfaction, and system efficiency of patients with complex, long-term problems.**[21] Collaborative care has been used successfully for the management of common mental disorders such as depression, as well as for comorbidities cutting across multiple services, providers, and settings.[22] Collaborative care is closely related to a stepped care approach; some programs describe themselves as *collaborative stepped care*, in that they incorporate aspects of each approach within their interventions.[23] In the stepped care approach, patients typically start treatment with low-intensity, low-cost interventions. Treatment results are monitored systematically, and patients move to a higher-intensity treatment only if necessary. Programs seek to maximize efficiency by deploying available human resources according to need, reserving the most specialized and intensive resources for those with the most complex or severe problems.

The essential element of collaborative care is a multidisciplinary team approach that seeks to integrate primary care professionals and specialists. Collaborative care rests primarily on the presence of a case manager with enhanced responsibilities for integration of care across comorbid conditions. It starts with systematic identification of those in need, followed by close involvement of patients in joint decision-making regarding their care. It continues with the design of a holistic care plan that includes medication management and psychological interventions, and where appropriate, social care, with a streamlined referral pathway that allows patients to move easily from one service to another. There is provision for regular and planned monitoring of patients and systematic caseload reviews and consultation with mental health specialists regarding patients who do not show clinical improvement.[24]

Collaborative care is the best-evaluated model for treating common mental disorders in primary care. A recent Cochrane Collaboration review of 79 randomized controlled trials concluded that collaborative care for depression is consistently more effective than usual care; it has also been shown to be effective in a range of MNS disorders—anxiety disorders, post-traumatic stress disorder—and for improving general health outcomes. The evidence base for collaborative care is mostly from *high-income countries* (HICs), although evidence from LMICs is growing.[25] The MANAS study in Goa, India, showed that a lay counselor-led collaborative stepped care intervention for depression and anxiety disorders in primary health care settings led to substantial reductions in the prevalence of these disorders, suicidal behaviors, and days of work lost, compared with usual care.[23] The Home Care Program for the elderly people affected by dementia, showed benefits in reducing the caregiver burden and improving caregiver mental health in India.[26] In Chile, a multicomponent intervention lasting 3 months and comprising nine weekly sessions of psycho-educational groups, structured and systematic follow-up, and pharmacotherapy for women with severe depression, led by nonmedical health workers, demonstrated that at 6-months' follow-up, 70 percent of the stepped care group had recovered, compared with 30 percent in the usual-care group.[27] The program is being rolled out across Chile. A similar program subsequently tested among low-income mothers in postnatal primary-care clinics in Santiago, Chile, demonstrated significant improvement in the intervention group.[28]

These case studies described primarily focused on evidence generation and were conducted in a controlled setting. There are also several other case studies from a number of LMICs which demonstrate real-world implementation of this evidence-base. In the city of Sobral, Brazil, primary care practitioners conducted physical and mental health assessments for all patients as part of integrated primary care for mental health. Joint consultations are undertaken among mental health specialists, primary care practitioners, and patients. This model ensures good-quality mental health care, and it serves as a training and supervision tool whereby primary care practitioners gain skills that enable greater competence and autonomy in managing mental disorders.[16] A similar model is being practiced as part of the District Mental Health Programme in Thiruvananthapuram district, Kerala, India. Over time, the primary care centers have assumed responsibility for independently operating mental health clinics with minimal support from the mental health team.[16] The European Headache Federation and Lifting the Burden: the Global Campaign against Headache[29] has proposed a collaborative care model for the management of headache disorders. In this model, 90 percent of people consulting for migraine and tension-type headache can be diagnosed and managed by staff at the primary care level. In case of remaining 10 percent of the patients, common primary and secondary headache disorders can be recognized but not necessarily managed and then these can be referred to the next level, where physicians can provide more advanced care. Finally, specialists can provide advanced care to approximately 1 percent of patients first seen at the first-level and second-level facilities and can focus on the diagnosis and management of the underlying causes of all secondary headache disorders. A demonstration project based on this model is in Yekaterinburg, Sverdlovsk Oblast, Russian Federation,[30] and headache services in China have been designed on this model.[31]

The collaborative stepped care approach relies heavily on the introduction of additional human resources, identification of core competencies, adequate training

to ensure that these core competencies are fulfilled, and specialist support to maintain these competencies.

Strategy 2. Strengthening Human Resources for Mental Health through Task Sharing:

One of the main reasons for the substantial treatment gap for MNS disorders is the lack of a skilled workforce. In HICs, the number of mental health workers is often inadequate; in LMICs, the situation is dramatically worse, with an estimated shortage of 1.18 million workers.[32] The collaborative stepped care approach can be implemented only if skilled human resources are available at the different levels of service delivery.

Task-sharing Approach

Task-sharing is a human resource innovation in which the skills to deliver specific mental health care tasks are transferred to appropriately trained and supervised general health workers. This process helps in improving access to evidence-based mental health care and leads to more efficient use of these limited resources. This approach has been evaluated for mental health service delivery, and its efficacy has been established using rigorous evaluation methodologies.[23, 27, 33] Task-sharing is implemented through a collaborative care framework with four key human resources: the community health worker/case manager; the person with a mental health problem and family members; the primary or general health care physician; and the mental health professional.[34] The overall shortage of human resources can be addressed by introducing newly skilled non-specialist health workers at community level; reorienting medical officers and paramedical staff to integrate mental health interventions; and redefining the role of specialists from service provision to leadership, training, and supervision of mental health programs.

The task-sharing approach is at the heart of establishing the collaborative stepped care models; the most crucial element in this approach is the availability of a case manager. Several global case studies have found that primary care for mental health is usually most effective where a mental health coordinator/case manager is responsible for overseeing integration.[16] These case managers can play a crucial role in screening; engaging; educating patients

and family members; maintaining close follow-up; tracking adherence and clinical outcomes; and delivering targeted, evidence-based, psychological interventions, such as motivational interviewing, behavioral activation, problem-solving, or interpersonal therapy.[35] The case managers can serve as the link between the primary care and self-care platform and can work under the close supervision of the medical officers.

Competency-based and Continuing Education

Primary care workers function best when their tasks related to mental health service delivery are limited and achievable. The most common reasons for failure to integrate mental health care into primary care programs are the lack of adequate assessment and overly ambitious target setting without the necessary customization of the detailed activities, and a full and explicit agreement on the targets and activities needed to achieve them.[35] A shift away from knowledge-based education to competency-based education is needed. This approach mainly focuses on the skills of providers, with the ultimate goal of improving patient outcomes. *Competency* is defined as an attribute of an individual human resource and the ability of that worker to deliver an intervention to a desired performance standard based on the acquired knowledge and skills. *The Institute of Medicine's* (IOM) Forum on Neuroscience and Nervous System Disorders have identified core competencies that specialized and nonspecialized primary care providers might need to help ensure the effective delivery of services for depression, psychosis, epilepsy, and alcohol use disorders in sub-Saharan Africa.[36]

Pre-service and in-service training of primary care workers on mental health issues is an essential prerequisite for the integration of mental health into primary care platforms. The training, to the extent possible, should happen in primary care or community mental health care facilities, to ensure that practical experience is gained and that ongoing training and support are facilitated.[16] The effects of training are nearly always short-lived if health workers do not practice newly learned skills and receive ongoing specialist supervision. A trial from Kenya did not find any impact of the training program of medical officers on improvement in diagnostic rates of mental

disorders.[37] A quasi-experimental study from Brazil had similar findings and noted that wider changes in the system of care may be required to augment training and encourage reliable changes in clinical practice.[38] Ongoing support and supervision from mental health specialists are essential. Case studies from Australia, Brazil, and South Africa have demonstrated that a collaborative stepped care approach in which joint consultations and interventions occur between primary care workers and mental health specialists increases the skills of primary care workers and builds mental health networks.[16] It is absolutely imperative to sustain the competencies of the primary care workers and new information technology enabled platforms such as skype and social media applications such as Facebook and Whatsapp can be potentially used for online distant supervision by the specialist. In addition to this decision support algorithms enabled by mobile health, cloud-based electronic health records that can be accessed and updated by any provider, automated medication and appointment reminders offer new opportunities to address systemic barriers to improving coverage of service by the trained human resource.[3]

Specialist Transitioning

Specialists, especially in LMICs, are usually engaged in service delivery. It is imperative to make a transition from providing clinical services to training and supervising the primary health care staff, and providing direct clinical interventions judiciously and sparingly. In two projects focusing on integrated primary care for mental health in city of Sobral, Brazil, and Sembabule district of Uganda, specialists visited primary care settings and assessed patients together with medical officers in primary care. Over time, psychiatrists started taking less active roles while general practitioners assumed added responsibilities, under the supervision of the psychiatrists. Specialists can interact with primary care staff via referral and back-referral.[16]

Planning and Consultation

Involving primary health care staff in overall program planning and rollout process enhances ownership and commitment to achieve the planned outcomes within agreed timelines.[35] Consultations with general practitioners was demonstrated to be one of the key factors in

success of the new mental health services in Australia.[16] Decisions must be made after careful consideration of local circumstances; this requires consultation with policy makers, as well as users of mental health services and the families and the primary care staff.

Psychotropic Medications

It is important to ensure that primary care staff members have the appropriate permission to prescribe psychotropic medications, and they must be adequately trained to perform this task. In many countries, nurses and even general physicians are not permitted to prescribe psychotropic medications. If access to psychotropic medications is to be improved, then initiatives to allow primary care nurses to prescribe psychotropic medications need to be promoted and undertaken, provided appropriate training and supervision is conducted. In Belize, psychiatric nurse practitioners have been given additional prescription rights. In Uganda, general primary care nurses are permitted to prescribe psychotropic medication to patients who require continued medication on the recommendation of a mental health professional.[16]

Strategy 3. Integrating Mental Health into Existing Health Care Delivery Channels:

Expansion and integration of mental health services in primary health care can be achieved by using existing service delivery for maternal and child health, non-communicable diseases, and HIV/AIDS and tuberculosis.[39]

Maternal and Child Health Programs

Promising evidence suggests the benefits of the integration of maternal mental health into maternal and child health (MCH) programs.[40] The Thinking Healthy Programme in Pakistan is a simple and culturally appropriate intervention for integrating depression care in a MCH program. The intervention is child-centered, ensuring buy-in from the families and avoiding stigmatization. It is woven into the routine work of the community health workers, so it is not seen as an extra burden but supports the routine work. The Thinking Healthy Programme has been further adapted so that it can be used universally for all women rather than only depressed women.[40]

The Perinatal Mental Health Project in the Western Cape Province of South Africa developed a stepped care

intervention for maternal mental health that is integrated into antenatal care in three primary care midwife obstetric units.[41] This case study clearly demonstrates that onsite, integrated mental health services increase can access for women who have scarce resources and competing health, family, and economic priorities.[41]

Parenting skills training aims to enhance and support the parental role through education and skills enhancement, thereby improving the emotional and behavioral outcomes for children. Primary health care workers can play a significant role in this training. The use of scarce professional resources to train parents is a cost-effective use of resources and can be integrated in primary care services. Several systematic reviews have shown parent skills training to be effective for reducing both internalizing and externalizing problems in children,[42, 43] as well as reducing the risk of unintentional childhood injuries[44] and improving the mental health of parents.[45]

Noncommunicable Disease Programs

Existing service delivery platforms for noncommunicable diseases are also promising entry points for the integration of mental health into primary care. The collaborative care models discussed demonstrate a strong evidence base for integration in primary care settings. In North America, TEAMcare, US, and TEAMcare, Canada provide team-based primary care for diabetes, coronary heart disease and depression. About 1400 people have received TEAMcare, with a trial showing improvements in medical disease control and depression symptoms.[46] In the United Kingdom, *3 Dimensions of Care for Diabetes* (3DFD) uses a team consisting of a psychiatrist and a social worker from an nongovernmental organization embedded in the diabetes care team to integrate medical, psychological, and social care for people with diabetes and mental health problems, and/or social problems, such as housing and debt.[47] The National Depression Treatment Programme in Chile integrated depression care with more traditional primary care programs for the management of hypertension and diabetes within a network of 520 primary care clinics.[48] In Myanmar and in several LMICs, epilepsy has been included as part of the process of local adaptation and implementation of the WHO's package of essential noncommunicable disease interventions in primary care.[24]

HIV/AIDS and Tuberculosis Programs

The WHO's *Integrated Management of Adult and Adolescent Illness* (IMAI) is a broadly disseminated health care strategy that addresses the overall health of patients with HIV/AIDS and co-occurring tuberculosis; clear opportunities exist for integration of mental health in this program.[49] In South Africa, the government has published integrated guidelines for all primary health workers, including HIV/AIDS; major non-communicable diseases; and a range of mental health problems, including depression, anxiety, mania, substance abuse, and psychosis. This guideline, called *Primary Care 101* (PC101),[50] is used by the national Department of Health as part of a primary care revitalization program to deliver integrated care within a chronic disease management framework.[51]

Resource Estimation

In order to achieve the successful and sustainable scale-up of effective interventions and innovative service-delivery strategies mentioned above, it is critical to conduct an analysis of resource estimation (financial as well as human) required to operationalize components of collaborative care model, build and sustain the competencies of the human resources and engage with all the key stakeholders including users and community members. This exercise is beyond the scope of this paper, but has been carried out as part of the Disease Control Priorities 3rd edition[4] and for five low and middle-income countries in the *Programme for Improving Mental health care* (PRIME).[52]

Quality of Care for MNS Disorders

Despite the strong and growing knowledge base for delivery of mental health services, the 'treatment gap' for MNS disorders remains unacceptably large, with over 90% of people with mental disorders in LAMICs going without treatment.[53] This 'treatment gap' is not just a quantitative phenomenon; it also contains an important 'quality' of care dimension. There is a significant gap between what is known about effective treatment and what is actually provided to and experienced by consumers in routine care.[54] Quality in health care has been defined by the Institute of Medicine as 'the degree to which health care

services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge'.[55] Good quality care is (or should be) effective, efficient, equitable, timely, person-centered, safe and delivers a positive patient experience.[55] In the language of Universal Health Coverage, it is the difference between contact coverage and effective coverage; that is, substantial improvement in access to care need to be also accompanied by improvement in the quality of service delivery.

Inadequacy of resources and low priority given to the MNS disorders might lead one to think that consideration of the 'quality' of care be subservient to the quantity of available and accessible services. However, quality improvement mechanisms ensure that available resources are well utilized—in the sense that those in contact with services actually derive appropriate benefit from evidence-based interventions. Moreover, good quality services help to build people's confidence in making use of mental health care interventions, thereby increasing the likelihood of seeking the care that they need.[56] Low quality services, on the other hand, lead people with MNS disorders to experience human rights violations and discrimination in health-care settings. In many countries, the quality of care in both inpatient and outpatient facilities is poor or even harmful and can actively hinder recovery.[57] Quality improvement frameworks and guidelines for LAMICs have been developed in the form of a WHO guidance package for quality improvement in mental health service.[58] It provides an integrated resource for the planning and refining of mental health systems on a national scale.[56]

Conclusions

The key points for effective and efficient delivery of MNS services are as follows:

- **To deliver interventions for MNS disorders, the focus needs to move from vertical programs to horizontal health service platforms.**

- **The WHO pyramid framework of self-care, primary care, and specialist care continues to provide a useful approach for understanding potential delivery channels.**

- **A set of evidence-based interventions within this framework can be identified for promotion/prevention, identification/case detection, and treatment/care/rehabilitation interventions.**

- **The delivery of these interventions requires an approach that embraces public health, systems, and whole of government principles.**

- **The key strategies for this delivery are implementing collaborative stepped care, strengthening human resources, and integrating mental health into general health care.**

- **Finally, it is not only important to improve access to health services for MNS disorders but also to focus on improving the quality of care delivered.**

Recommendations for policy makers include adopting these principles and strategies using a platform-wide approach. Policy makers need to engage with a wide range of stakeholders in this process and make use of the best available evidence in a transparent manner. ❱❱

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Declarations

Hatherleigh's Note: *Additional typeface treatment was added to text for emphasis. Supplementary title page information, CME, Best Practices, and medication trade names were also included.*

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L003372

Multiple-Choice Questions

33. Elements of a mental health care delivery platform include:

   A.   self-care and informal health care.

   B.   primary care.

   C.   specialist health care.

   D.   All of the above.

34. Evidence-based interventions for health care delivery include:

   A.   promotion and primary prevention.

   B.   identification and case detection.

   C.   treatment, care, and rehabilitation.

   D.   All of the above.

35. All of the following statements are correct, *except*:

   A.   Primary care serves as the first level of care within the formal health care system.

   B.   A strong evidence base supports integrated services across different delivery channels of the health care platform.

   C.   Single service delivery channels are equipped to meet all of the mental health needs that present in practice.

   D.   Forensic psychiatry is a type of specialist service in health care.

36. Collaborative care is an evidence-based approach to improve the management of MNS disorders at the level of:

   A.   self-care.

   B.   informal care.

   C.   primary and specialist care.

   D.   All of the above.

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Best Practices in CME

Closing the Treatment Gap for Mental, Neurological and Substance Use Disorders by Strengthening Existing Health Care Platforms: Strategies for Delivery and Integration of Evidence-based Interventions

By Rahul Shidhaye, MBBS, MD; Crick Lund, BA, BSocSci, MA, MSocSci, PhD;

and Dan Chisholm, PhD

ID#: L003372

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

This lesson outlines the main elements and features of a mental health care delivery platform and its delivery channels. A set of evidence-based interventions within the WHO pyramid framework of self-care, primary care, and specialist care have been identified. The delivery of these interventions requires an approach that puts into practice key principles of public health, adopts systems thinking, promotes whole-of-government involvement and is focused on quality improvement.

Key Point 1: Background

To deliver interventions for MNS disorders, the focus needs to move from vertical programs to horizontal health service platforms. The WHO pyramid framework of self-care, primary care, and specialist care continues to provide a useful approach for understanding potential delivery channels.

Key Point 2: Interventions within the Framework

A set of evidence-based interventions within this framework can be identified for promotion/prevention, identification/case detection, and treatment/care/rehabilitation interventions.

Key Point 3: Delivery of Evidence-based Interventions

The delivery of these interventions requires an approach that embraces public health, systems, and whole of government principles.

Key Point 4: Strategies to Effectively Deliver Care

The key strategies for this delivery are implementing collaborative stepped care, strengthening human resources, and integrating mental health into general health care.

Notes

Recent Advances in Psychological Therapies for Eating Disorders

Glenn Waller, DPhil, MClinPsychol, BA

No commercial support was used in the development of this CME lesson.

KEYWORDS: Eating disorders • Psychological Therapies • Family-Based Treatment

LEARNING OBJECTIVES: Readers will review the various forms of psychological therapies in the treatment of eating disorders such as *cognitive-behavioral therapy* (CBT) and family-based treatment, and assess their efficacy and outcomes. Readers will also review other forms of adjunctive therapies that are useful to include patients' treatment plan.

LESSON ABSTRACT: Recent years have seen substantial consolidation and development of the evidence base for psychological therapies for eating disorders. This review summarizes the key changes over that time period. Specific forms of cognitive behavioral therapy and family-based treatment have consolidated and extended their positions as treatments of choice despite the development of novel approaches. However, there is still a significant need for further development and testing to improve recovery rates, particularly in anorexia nervosa.

COMPETENCY AREAS: This purpose of this lesson is to review and expand the knowledge base of psychological therapies for the treatment of eating disorders in clinicians.

Introduction

How far have we progressed in the treatment of eating disorders during the current decade? In a previous review,[1] it was suggested that developments were necessary. There has been little advance in some areas that were identified as targets for further research, such as treatment matching and the role of pharmaceutical interventions.[2] However, there have been substantial developments in psychotherapies and their outcomes since 2009. This review will summarize the evidence relating to these advances.

The psychotherapies considered here are designed to treat the eating disorder in and of themselves. However, there are also symptom-based and adjunctive approaches that are designed to address specific elements of the eating disorder (e.g., cognitive flexibility) without the expectation that they will bring about remission on their own. Recent evidence regarding some of those approaches will be considered separately below.

Psychotherapy Outcomes: Some Consolidation, Some Change

Therapeutic Context:

The setting in which psychological therapies is carried out is an important issue and is at least partly determined by local health practices. For example, in some countries, individuals with bulimia nervosa are routinely treated in a combination of in- and out-patient settings, whereas in others it is very rare for them to be treated as in-patients at all. Thus, findings need to be understood in their context. A particular issue in interpreting treatment outcomes is the need to understand the degree of in-patient work that has been involved in the treatment of patients with anorexia nervosa. In-patient care for anorexia nervosa is not a predictor of better outcomes than treatment in less intensive settings and is substantially more expensive.[3, 4] suggesting that its use should be confined to medical need (e.g., preliminary weight gain, medical stabilization). Similarly, there is little to suggest that any specific psychotherapy is more effective in an in-patient setting.

Another issue is whether the delivery modality makes a difference in terms of outcomes. In short, there has been little change here. Different forms of self-help and group treatments are less effective than face-to-face individual therapy, as has been the case since the different modalities were developed. More recent work has examined the potential of electronic media (e.g., smartphone apps) for delivering therapy. However, to date, there is little robust evidence that this is an effective approach.[5, 6] Therefore, unless otherwise specified, it should be noted that the following conclusions usually are developed from, and are more applicable to, out-patient treatment settings.

Younger cases

Among children and adolescents who have had anorexia nervosa for a relatively short period of time, specific types of *family-based treatment* (FBT) have a good recovery rate, particularly by the time of follow-up.[7] However, among younger anorexia nervosa cases, there is some evidence that this superiority over individual therapy is not maintained by the time of follow-up.[8] Regardless, it remains possible to conclude that FBT is superior to individual approaches in terms of either speed or level of recovery. There are suggestions that this approach can be delivered in fairly diverse ways (e.g., fewer sessions, in multi-family settings) as long as the core therapeutic elements remain in place (e.g., the family taking charge of the patient's eating).

Other individual-based approaches have been tested with this age group in recent years—particularly, *cognitive-behavioral therapy* (CBT). There is now evidence that CBT can be a useful approach for adolescents with either underweight or non-underweight eating disorders.[9-11] **However, it should be noted that FBT has the more immediate benefit when compared directly with CBT for adolescents with bulimia nervosa, although it was not statistically superior to CBT at follow-up.[12]** Therefore, in this age group, CBT should be considered as an alternative that can be used only where FBT is not possible or indicated or where FBT has failed to be effective. There is also a need for further exploration of methods suited to childhood cases.

Adult Cases:

The role of cognitive-behavioral therapy. **The most powerful additional evidence that has emerged in the past five years is a series of articles that reinforce and extend the place of CBT as the leading approach in the treatment of eating disorders in adults. CBT in different forms was already established as the front-line treatment for bulimia nervosa and binge**

eating disorder.[13] Since then, a series of studies[14-19] using Fairburn's enhanced form of CBT (CBT-E) have demonstrated the following:

- **CBT-E is effective for normal-weight bulimia nervosa and atypical eating disorders; approximately half of patients remit and remain well.**

- **Patients with anorexia do moderately well with CBT-E (approximately 30% entering treatment recover by the end of out-patient therapy, and a somewhat higher rate by the end of in-patient treatment).**

- **CBT-E is more effective than *interpersonal psychotherapy* (IPT) and psychodynamic therapy for normal-weight cases. One study[20] has suggested that a focal psychodynamic therapy for anorexia nervosa is as effective as CBT-E by the point of follow-up, but so was the "treatment-as-usual" condition, perhaps because the effects of all the therapies were obscured by a relatively high level of in-patient treatment.**

Caveats. These conclusions about CBT need to be considered in the light of certain caveats. First, there is no direct comparison of CBT-E with existing versions of CBT, so it is not clear that CBT-E represents an improvement over existing CBT approaches or simply a wider application of core CBT methods across eating disorders.

Second, CBT-E has changed over time; in its early incarnation, it had two forms ("broad" and "focused"). However, the lack of difference in outcomes across these forms was followed by the more recent adoption of a hybrid version, based on the original 'focused' form but incorporating the "mood intolerance" module from the "broad" version.[21] Therefore, understanding the impact of CBT-E requires clarity about which form is under consideration.

Third, other structured therapies that are based on a cognitive model but include other elements (e.g., affective) can be as effective as CBT-E in non-underweight patients.[22] There remains the possibility that the level of structure in a therapy is key to good outcomes, perhaps as much as the content.

Finally, the nature of the CBT that is being delivered needs to be considered. For example, one study[23] concluded that out-patient CBT was not effective for delivering remission in long-standing anorexia nervosa cases (although the chronicity of the individuals' disorders was not greater than that of some patients in other studies). However, although the chronicity of eating disorders is related to the likelihood of spontaneous recovery,[24, 25] the impact of chronicity on treatment outcome has not yet been proven.[26] Possibly more importantly, the comparability of this variant of CBT with others is limited by the fact that the researchers de-emphasized weight gain as a target of treatment, making it secondary and dependent on the patient's enthusiasm to engage in it. Thus, the conclusion that CBT is not effective in longer-standing cases is not yet proven, as the key outcome variable of weight gain[27] was replaced with a primary outcome of improved quality of life.

- *Other therapy developments for adults with anorexia nervosa.* **Though better than they were five years ago, CBT's outcomes for anorexia nervosa remain disappointing. However, that disappointment needs to be understood in the context of the even poorer outcomes of other therapies for anorexia nervosa that have been reported in recent years. These include the following:**

- *Specialist supportive clinical management* **(SSCM). Early SSCM findings were promising, suggesting better outcomes than CBT or IPT for anorexia nervosa.[28] However, those differences disappeared or reversed at long-term follow-up,[29] suggesting that SSCM might be a therapy that needs to be delivered long-term to maintain its effects. Subsequent studies have suggested a lower recovery rate than for CBT-E;[17] the out-patient recovery rate was about 15%.[30]**

- **The *Maudsley model of anorexia nervosa treatment for adults* (MANTRA). MANTRA is based on a relatively elaborate theory compared with CBT, on the assumption that CBT is too simplistic to deal with the multiplicity of different pathological factors in anorexia nervosa cases. However, initial**

findings suggest that it is notably less effective than CBT-E; the recovery rate is similar to that of SSCM.[30]

- *Dialectical behavior therapy* (DBT). A version of this therapy (termed radically open-DBT) has been developed for anorexia nervosa, focusing on the compulsive pathology of such cases. To date, it has been tested only in a clinical case series of in-patients, with a large number of missing data.[31] According to the method of selecting patients for the final analysis, approximately 15-20% of those entering treatment remitted by the end.

Thus, although the 30% recovery rate for anorexia nervosa when using CBT-E is undoubtedly weaker than for non-underweight cases, it is noticeably stronger than the recovery rates for other therapies, even where pre-treatment characteristics such as age, duration of disorder, and body mass index are comparable. However, most of the therapies outlined above have a reasonable "partial recovery/improvement" rate for anorexia nervosa,[17, 29-31] suggesting that each has potential to be developed to be more powerful. Efforts to improve all psychological therapies for anorexia nervosa are as important now as they were a decade ago.

Adjunctive and Symptom-Based Therapies

It is important to note that there are treatments that are effective at addressing elements of eating pathology, even though they are not expected to produce remission or recovery. Recent key developments in this domain are considered briefly here.

Nutritional Work:

Obviously, re-nourishment is not a psychological therapy in itself but is a treatment element that appears to be crucial in facilitating the impact of psychotherapies. Starvation/semi-starvation is a powerful maintaining factor in the eating disorders; it has an impact on biology, cognitions, emotions and social function. Those effects can be seen among normal-weight patients as well as those who are underweight. There is little doubt that restoring nutritional balance is important for recovery,

but it has recently been shown that nutritional improvements are important in terms of both positive changes in core cognitions[32] and psychosocial functioning, such as quality of life.[33] Therefore, nutritional changes appear to be necessary for psychotherapies to be effective for eating disorders.

Cognitive Remediation Therapy:

Cognitive remediation therapy (CRT) is increasingly used to address the cognitive inflexibility that is associated with eating disorders, particularly anorexia nervosa. The evidence to date[34] suggests that CRT is associated with greater cognitive flexibility in case series. There is also some evidence from randomized controlled trials that CRT is effective in relieving some aspects of eating pathology and in enhancing retention in other therapies,[35-37] although the benefits do not always appear to operate via the expected route of enhanced cognitive flexibility.[34] The evidence to date is promising, but conclusions will need to await further studies. Two key questions remain to be addressed. First, are the effects of adjunctive CRT associated with positive outcomes from other therapies? Second, is CRT valuable over and above the impact of re-nourishment of the starved patient?

Support for Carers:

It is important to remember that those with the eating disorder are not the only people to suffer from its effects. Carers for such patients also experience high levels of stress and distress. Acknowledging carers' needs has resulted in a range of individual and group support programs, intended to relieve those experiences. Those interventions are well received[38] and are effective in reducing carers' distress,[39] although it remains to be determined whether they have any clear benefit in terms of patients' symptoms.

Conclusions

There have been substantial developments in the field of psychological therapies for eating disorders since this decade began. To summarize, there has been:

- **consolidation of the position of CBT for bulimia nervosa and binge eating disorder,[16, 18, 19]**

- **some evidence that other therapies for normal-weight cases can be as effective as CBT,**[22]

- **enhanced evidence that FBT is the treatment of choice for younger cases,**[7, 8, 12]

- **improvement of the reach of CBT to other eating disorders, including among adolescents,**[11, 14-18]

- **clearer evidence for some adjunctive approaches, even if their target is not recovery,**[32-39] **and**

- **disappointment that treatment outcomes for adults with anorexia nervosa are still weaker than for non-underweight cases, even though there are differential effects for different therapies.**[17, 23, 29-31]

Between them, these developments offer both possibilities and challenges. Clinicians have clearer guidance as to what is likely to be effective for their patients, and should be encouraged to work with that information (in the absence of any clear heuristics for treatment matching, apart from age). There remain substantial deficits in our treatment of eating disorders, particularly for cases of anorexia nervosa. **Although the development of therapies such as MANTRA and radically open-DBT has been important, at present their benefits are not yet comparable to those of FBT and CBT.** CBT and FBT themselves will need further development (e.g., recent evidence that a planful response to a lack of early change is beneficial in FBT for adolescents with anorexia nervosa).[40] Additionally, other therapies will need to be developed and tested further over the next decade, particularly where they show some promise already in terms of symptom reduction and partial or complete recovery.[20, 22, 28, 30, 31, 34]

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Competing interests:

The author declares that he has no competing interests.

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Multiple-Choice Questions

37. **Which therapeutic method has a more immediate benefit for adolescents with bulimia nervosa?**

    A. Cognitive-behavioral therapy

    B. Family-based treatment

    C. Interpersonal psychotherapy

    D. Exposure-based therapy

38. **Which one of the following is the leading approach to treating eating disorders in adults?**

    A. Pharmacotherapy

    B. Cognitive-behavioral therapy

    C. Interpersonal therapy

    D. None of the above

39. **What has Fairburn's enhanced form of CBT (CBT-E) demonstrated?**

    A. CBT-E is effective for normal-weight bulimia nervosa and atypical eating disorders.

    B. Patients with anorexia do moderately well with CBT-E.

    C. CBT-E is more effective than *interpersonal psychotherapy* (IPT) and psychodynamic therapy for normal-weight cases.

    D. All of the above.

40. **Which one of the following statements is correct regarding psychological therapies for eating disorders?**

    A. The *Maudsley model of anorexia nervosa treatment for adults* (MANTRA), based on the assumption that CBT is too simplistic to deal with the multiplicity of different pathological factors, has proven more effective than CBT-E.

    B. Treatment with *specialist supportive clinical management* (SSCM) suggest better outcomes than CBT or IPT for anorexia nervosa at long-term follow-up.

    C. Outcomes of radically *open-dialectical behavior therapy* (DBT) have shown that its benefits are not yet comparable to those of FBT and CBT.

    D. All of the above.

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Best Practices in CME

Recent Advances in Psychological Therapies for Eating Disorders

By Glenn Waller, DPhil, MClinPsychol, BA

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This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The psychotherapies reviewed in this lesson such as: *cognitive-behavioral therapy* (CBT), *cognitive-behavioral therapy enhanced* (CBT-E); *family-based treatment* (FBT), and others are designed to treat the eating disorder in and of themselves. Clinicians will also review symptom-based and adjunctive treatment approaches that are designed to address specific elements of the eating disorder.

Key Point 1: Leading Treatment Approach

Cognitive-behavioral therapy is the leading approach to treat eating disorders in adults.

Key Point 2: Treatment in Children and Adolescents

In children and adolescent populations, family-based treatment promises a more immediate benefit when compared directly to **CBT**, although this finding was not statistically superior to **CBT** at follow-up.

Key Point 3: Other Therapies

Therapies such as *Specialist supportive clinical management* (**SSCM**), the *Maudsley model of anorexia nervosa treatment for adults* (**MANTRA**), and *Dialectical behavior therapy* (**DBT**) have shown some promise but more research is needed to demonstrate effectiveness at long-term follow-up.

Key Point 4: Adjunctive Therapies

Adjunctive therapies such as nutritional work, cognitive remediation therapy, and support for carers show promising results when used to address eating pathology, although the end result is not expected to produce recovery. necessitate

Notes

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Psychiatrists as Expert Witnesses

Jennifer Piel, JD, MD; Phillip Resnick, MD

No commercial support was used in the development of this CME lesson.

KEY WORDS: Expert witness • Fact witness • Testimony • Daubert • Frye • Qualifications

LEARNING OBJECTIVES: The role of psychiatrists as expert witnesses will be discussed in this lesson. This lesson will provide guidance for testifying and enable clinicians to understand: (1) the circumstances calling for psychiatric expert witnesses, (2) the difference between expert and fact witnesses, and (3) the bases for expert qualification.

LESSON ABSTRACT: Psychiatrists are commonly asked to participate in court proceedings. Not all psychiatrists feel comfortable in this setting. This may be due, at least in part, to being unfamiliar with the legal process and one's role when serving as a witness. This lesson reviews the types of witnesses in court and gives specific guidance for the psychiatric expert witness.

COMPETENCY AREAS: This lesson aims to address the gaps in learning in medical knowledge and professionalism. Further, it will help providers gain knowledge in the area of expert witness testimony. Many psychiatrists feel uncomfortable when confronted with issues related to the legal system, including serving in the role of an expert witness. Upon conclusion of reading this lesson, readers should have a better understanding of the circumstances that may call for psychiatric expert witnesses. The lesson also reviews the distinction between fact and expert witnesses, how a witness is qualified as an expert in court, types of witness testimony, and tips for expert witness testimony.

Introduction

Psychiatrists may be called to give expert opinions on topics relevant to mental health and the law. When serving as an expert witness, a psychiatrist's role is to educate members of the court about key psychiatric issues in the legal case. Psychiatrists may be involved in civil cases and issue opinions on topics such as psychiatric malpractice, psychological harm in personal injury cases, and fitness for duty. In the criminal setting, psychiatrists may be asked to evaluate and opine on such issues as a defendant's competency to stand trial, insanity, or competence to be executed. In fact, psychiatrists are among the most common experts to testify in court cases.[1]

Not all psychiatrists feel comfortable giving expert opinions and testimony. Similarly, some psychiatrists are better at serving as expert witnesses than others. However, with preparation and awareness of the legal system, even the novice expert witness can aid the court in its understanding of mental health issues. This lesson reviews the role of the psychiatric expert witness, expert qualifications, and techniques to improve witnesses' comfort level and effectiveness when serving as experts.

Table 1:
Examples of Case Types with Psychiatric Expert Testimony

Civil Cases	Criminal Cases
• Child custody	• Criminal competencies
• Civil commitment	• Dangerousness/conditional release
• Civil competencies	• Death penalty mitigation
• Disability/workman's compensation	• Insanity
• Emotional injuries	• Miranda waiver
• Fitness for duty	
• Malpractice/professional liability	

Fact and Expert Witnesses

Although all psychiatrists have expertise in the field of psychiatry, this training alone may not qualify a psychiatrist as an expert witness in court. There are two types of witnesses that appear in court: fact witnesses and expert witnesses. Each type of witness has specific roles in the courtroom.

Fact Witnesses:

Fact witnesses testify as to their direct observations. They are called to testify due to their direct participation with a party or event related to a legal case. Take, for example, a psychiatrist who assessed and treated a patient after a motor vehicle accident. In this example, the treating psychiatrist may be called to testify about the patient's presenting complaints, diagnosis, number of appointments, medications prescribed, and side effects experienced.

While serving as fact witnesses, psychiatrists do not ordinarily render opinions, except under limited circumstances. In a minority of jurisdictions, the court may ask treating psychiatrists to state an opinion, particularly when the opinion is based on an actual perception by the treating psychiatrist. Compared to expert witnesses, treating clinicians are less likely to be viewed as "hired guns." Their testimony may be considered more credible by the trier of fact (judge or jury).

Expert Witnesses:

Expert witnesses are witnesses who testify because their special knowledge or experience lends expertise to the issues in a legal proceeding. Their testimony is based on their special knowledge, rather than any prior involvement with a party or direct participation in the events associated with a legal case. **Expert witnesses are commonly voluntarily retained by attorneys or the court, and they receive remuneration for the services they provide associated with the case.**

The expert's knowledge must be viewed as being beyond that normally possessed by the average person and beyond direct observation. **Experts may draw inferences and express opinions that have legal significance.** For example, a psychiatric expert could testify in a medical negligence case and give an opinion as to the cause of the claimant's injuries. As such, a psychiatric expert witness may educate the trier of fact about relevant facts, as well as provide conclusions about symptoms, causation, and prognosis.

Psychiatrists' conclusions on legal issues are mere opinions in the courtroom. Juries are instructed to decide for themselves how much weight to give the testimony of

each witness. In practice, the trier of fact may disregard the psychiatric opinion.

Table 2:
Fact and Expert Witnesses

Similarities Between Fact and Expert Witnesses	Differences Between Fact and Expert Witnesses
• May testify in court proceedings	• Experts must be "qualified" as experts by the court
• Have information to aid the trier of fact	• Experts provide opinion testimony
• Take an oath to tell the truth before testifying	• Experts are typically retained by attorney or court
• Not permitted to testify about hearsay absent recognized exception	• Experts receive financial compensation for their services related to the court case
	• Experts give opinions with reasonable medical certainty

Dual Role:

When a treating psychiatrist assumes both clinical and expert roles for a single patient, the psychiatrist forms a dual relationship with the patient. This scenario can present conflicts of interest and compromise the treatment relationship. In the treatment context, the psychiatrist's primary duties are to the patient, and the psychiatrist is commonly in a position of advocate for the patient. In contrast, as an expert witness, the psychiatrist has a responsibility to strive toward objectivity in rendering opinions in the service of justice.

Although the dual role is not unethical *per se*, it is important for psychiatrists to recognize that it can have professional and ethical implications. Commentary in the American Academy of Psychiatry and the Law's Ethics Guidelines for the Practice of Forensic Psychiatry states:

> Forensic evaluations usually require interviewing corroborative sources, exposing information to public scrutiny, or subjecting evaluees and the treatment itself to potentially damaging cross-examination. The forensic evaluation and the credibility of the practitioner may also be undermined by conflicts inherent in the differing clinical and forensic roles. Treating psychiatrists

should therefore generally avoid acting as expert witnesses for their patients or performing evaluations of their patients for legal purposes. [2]

Pre-trial Involvement

The expert's involvement in a legal case typically begins well in advance of the trial. When first contacted by an attorney, the psychiatrist should clarify the role that he or she is being asked to serve. Not all experts are hired with the goal of testifying at trial. Does the attorney want an independent medical examination? Does the attorney anticipate any testimony at trial? In some case, attorneys will retain consulting (non-testifying) experts to assist legal counsel with the preparation of their case.[3] These consulting experts help with trial strategy.

When retained as a testifying expert, the psychiatrist should:

1. **Make clear the question that he or she is being asked to answer. Although this may seem straightforward, the attorney may not have thought about specific issues. For example, in a criminal case, the attorney may ask for a "mental evaluation," which could mean an opinion about the defendant's competency to stand trial, sanity at the time of the act, or psychiatric factors for mitigation of penalty, among others.**

2. **Educate the attorney about tasks or questions that are not within their scope of the psychiatrist's expertise. Some attorneys have little experience with psychiatric experts and are not clear about the type of assessments that psychiatrists can provide in contrast with psychologists.**

3. **Obtain from the retaining attorney any legal standard on which the expert opinion is to be based. Legal standards vary by jurisdiction.**

4. **Gather the appropriate database of information. The database of materials may include prior psychiatric and medical records; school, employment, and military records; court records; police and witness reports; interviews with collateral participants; and psychological testing. The relevant sources of information**

and need for collateral will depend on the nature of the specific case.

5. **Conduct a personal interview of the evaluee when possible and relevant. Some cases, such as claims of psychiatric malpractice after a patient suicide, will not include an interview. In other cases, it will be important for the expert to conduct a psychiatric interview with attention to the mental status examination and inquiry into the areas relevant to the specific legal question at issue in the case.**

6. **Consider the diagnosis of malingering. Utilizing multiple sources of information is useful to identify inconsistencies and areas of agreement in the evaluee's position.**

7. **When asked, prepare a written report. The report should include a well-reasoned opinion on the legal issue by applying the facts to the appropriate legal standard.**

Admissibility of Expert Witnesses

For a person to be admitted to testify as an expert in court, the judge will first determine whether the person's expertise will assist the trier of fact in the case at issue. Then, the judge determines whether the person has the appropriate specialized knowledge or other qualifications. **It is the person's qualifications, not his/her title or degree, that counts.**

The *Federal Rules of Evidence* (FRE) govern the admissibility of expert witness testimony in federal courts. The FRE 702 (FRE 702) identifies the bases for which an expert may be qualified as an expert:

> **If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise.[4]**

Many state courts have adopted similar rules. Before enactment of the FRE, federal courts determining the admissibility of scientific or other technical testimony relied on the standard articulated in *Frye v. United States*

(1923).[5] Under *Frye*, the court considered whether the scientific principle or technique that formed the bases of the expert's testimony was "generally accepted" in the relevant field. Knowledge of the *Frye* standard is important because many *state courts* retain this standard. In addition, it remains as one consideration under the federal standards.

Another case, *Daubert v. Merrell Dow Pharmaceuticals* (1993),[6] superseded *Frye* in the federal system, stating that FRE 702 requires the trial judge to ensure that scientific evidence is relevant and reliable. Many states also have adopted the *Daubert* approach. In *Daubert*, the Supreme Court identified a list of factors to guide the assessment of reliability:

1. **Whether the theory or technique has been or can be reliably tested;**

2. **Whether it has been or can be subjected to peer review;**

3. **The known or potential rate of error of the technique;**

4. **The existence and maintenance of standards controlling its operation; and**

5. **The general acceptance of the technique.**

The *Daubert* decision emphasized the court's gatekeeping function. The trial court judge has great discretion in determining whether a person's specialized knowledge and experience relate to an issue in the case. Courts usually favor the admissibility of expert testimony on relevant issues, as both sides have an opportunity to counter it with opinions of their own expert. The presentation of contrary evidence, cross examination, and the burden of proof are means to challenge the expert testimony.

Expert Opinions

Expert witnesses generally have latitude in how they state their opinions in court. In many cases, experts may state an opinion, even if it is on an "ultimate issue" related to the case. The ultimate question is one whose answer is decisive in resolving the case. For example, in a case of medical malpractice, the psychiatric expert in such case could opine on the ultimate issue of the defendant clinician's negligence.

There is an exception to a mental health expert's ability to opine on ultimate issues. Under FRE 704(b), expert witnesses in federal criminal cases are prohibited from offering opinions about a criminal defendant's mental state in connection with any required element of the alleged crime:

> No expert witness testifying with respect to the mental state or condition of a defendant in a criminal case may state an opinion or inference as to whether the defendant did nor did not have the mental state or condition constituting an element of the crime charged or a defense thereto. Such ultimate issues are matters for the trier of fact alone.[7]

This rule comes into play primarily in the setting of cases where the criminal defendant has pleaded insanity. The impetus for this rule was concern that mental health experts could have too much influence over the trier of fact. The FRE 704(b) was enacted following John Hinckley's acquittal by reason of insanity on the charge of attempted assassination of President Reagan. The mental health expert can nevertheless testify as to the defendant's mental disease or defect and how the condition relates to the defendant's charged offense.[8] Many state courts do allow testimony on ultimate issues related to mental state or culpability.

Reasonable Medical Certainty

Psychiatric expert witnesses typically express their opinions to "a reasonable degree of medical certainty."[9] Although this is the most common phrasing, some jurisdictions may prefer "reasonable psychiatric certainty" or "reasonable psychological certainty" for mental health professionals. In most jurisdictions, this means that the expert expresses an opinion that is "more likely than not" to be true. Prudent psychiatric experts should confirm the standard in the applicable jurisdiction with the retaining attorney or court.

It is important to distinguish the standard for expert opinions (reasonable medical certainty) from the standard of proof for the case. The standard of proof reflects the guidelines the party required to prove the case must meet. The judge or jury weighs the evidence to determine whether the requisite standard of proof has been met.

The standard of proof required varies depending on the type of case involved. For example, in criminal cases, the prosecution must establish all parts of its case "beyond a reasonable doubt." In most civil cases, like medical negligence, the standard of proof is preponderance of the evidence, which requires a lower threshold of support than beyond a reasonable doubt. A medium standard, clear and convincing evidence, is used for certain cases involving deprivation of one's liberty interests, like child custody.

Types of Testimony

Depositions:

A deposition is sworn testimony taken before trial, usually taken outside of court. There are two types of depositions: evidence deposition and discovery deposition.

An evidence deposition is taken to preserve testimony when a witness will not be available at trial. Attorneys from both sides of the case may question the witness in a manner similar to direct and cross-examinations at trial.

A discovery deposition is taken to gather information prior to trial. Almost all questions are asked by opposing counsel. The attorney may ask broad questions with the goal of learning the facts and opinions of the opposing witness. The discovery deposition may also be used to identify weakness in the opposing expert's opinion or qualifications. Discovery depositions are common in civil cases. Psychiatric experts should take them seriously because they can have a large impact on settlement negotiations in the case and the deposition testimony may be used as a basis to impeach a witness (for example, by inconsistent statements) at trial.

Direct Examination:

On direct examination, the retaining party calls the expert witness to the stand to offer his/her opinion. Before experts give their opinion(s), the attorney will first lay a foundation for the subsequent testimony by eliciting the expert's qualifications and officially "qualifying" the witness as an expert using the criteria above.

The opposing attorney has a right to conduct a *voire dire* ("to speak the truth"), a cross-examination on the witness's background or methodologies, before the

witness continues with direct examination. Alternatively, the opposing counsel may accept the witness's qualifications. The judge decides whether the witness may testify as an expert.

When the expert is asked whether he or she has formed an opinion with reasonable medical certainty, the psychiatric expert should reply with a "yes" or "no" according to courtroom ritual. The witness is then asked to give their opinion and the rationale for the opinion. Narrative direct testimony has been effective in conveying information to the trier of fact.[10] However, this should be broken up by the attorney asking some questions to avoid long uninterrupted speech that may become tiresome.

A pre-trial conference is useful to the psychiatric expert and retaining attorney alike. This allows the psychiatrist and legal counsel to review those issues that should be brought out on direct examination and those issues most likely to be attacked during cross-examination. Whether expert witnesses should mention counterarguments to their own position during direct examination is open to debate. This is one topic that is useful to review with counsel prior to trial. One approach is to directly address these issues on direct examination, particularly if an opposing expert will testify.

When testifying, the psychiatrist should strive to communicate directly to the trier of fact. The use of simple language, rather than professional jargon, will increase the understanding of those not familiar with mental health terminology. If answers are too technical, boredom can cause the jury to lose interest. Eye contact with the jury helps the psychiatrist gauge the jury's understanding of what the expert is saying. While attempting to stay within these guidelines, expert witnesses should act naturally for their own personalities. A stilted performance detracts from the expert witness's appearance of sincerity.

Further, use of demonstrative evidence is useful to the psychiatric expert and should be used when possible. Demonstrative evidence differs from substantive evidence, which includes objects or materials that played a role in the incident at issue (e.g., murder weapon, x-ray). Demonstrative evidence may be referenced by the expert without formal admission into evidence. Examples of demonstrative evidence include visual aids, such as a list of key points of the expert's opinion or graphs showing

changes in the evaluee's depression screening scores before versus after an injury.

Table 3:
Tips for Direct Opinion Testimony

1. Have a pre-trial conference with the attorney to discuss the goals of testimony.
2. Consider explaining the problematic areas on direct examination (rather than waiting for attack on cross-examination) when afforded more opportunity to explain the issues and frame in one's own words.
3. Answer questions using plain language, not professional jargon.
4. Use demonstrative evidence when possible, such as visual aids of the expert's key points.
5. Never talk down to jurors.
6. Make eye contact with jurors.
7. Do not become an adversary; treat both attorneys with professional courtesy.
8. Answer the questions asked; be careful to avoid going beyond the question in direct or cross-examination because this may open up new areas for cross-examination.
9. Avoid over-advocacy. Experts may advocate for their **opinions** but should not become an advocate for the **party** that hired them.

Cross-examination:

Cross-examination is the questioning of a witness by the attorney opposing the one who asked the witness to testify in direct examination. Cross-examination is limited to the scope of testimony from the direct examination. The primary purposes of cross-examination are to cast doubt on the witness's direct testimony and point out the weaknesses of the expert's opinions.

The cross-examiner may seek to discredit an opposing expert witness by showing the witness to be unqualified, dishonest, or incompetent. Common categories for cross-examination include witness qualifications, expert bias, the adequacy of the evaluation underlying the expert's opinion, the validity of the methodology underlying the expert's opinions, and inconsistent statements. The psychiatric expert's qualifications may be attacked, for example, by revealing that the psychiatrist did not pass a board examination or has less training that the party's own expert.

Attorneys attempt to show bias in the expert witness by demonstrating that the expert witness has a history of having always been employed by one side (such as defense

firms). The appearance of bias is reduced when witnesses can say that they have experience in testifying for both sides. Other lines of inquiry aimed at showing bias or interest include demonstrating any personal relationship with an attorney or industry that has something to gain in the case, as well as the witness's fees. It is appropriate for psychiatric experts to be compensated for their time, just as the other courtroom participants (including legal counsel) are compensated for their services.

Another common area of attack in cross-examination is the adequacy of the psychiatrist's examination. A brief examination may be portrayed as insufficient to fully understand the situation. When the cross-examining attorney's own expert spent substantially more time on the case or reviewed more documents, for example, the attorney may attempt to show that the psychiatric expert was not thorough. A cross-examiner may seek to demonstrate this by asking, "What else would you have liked to review?" One response for the psychiatrist is to say that he or she had sufficient information to form an opinion to a reasonable degree of medical certainty.

The expert's methodology in formulating an opinion may be attacked, as well as psychiatry as a field. This latter is not likely to occur if the cross-examiner is also putting forth a psychiatric expert in the case, but may present an additional challenge when this is not the case. Faust (2011)[11] described the limited reliability of psychiatric examinations. Research demonstrated that different theoretical backgrounds predispose psychiatrists to reach different conclusions based on the same data. Psychiatric experts should be aware of the relevant literature and testing and be prepared to explain the bases for their opinions.

The cross-examiner may impeach an expert by demonstrating inconsistencies within an expert's report, between the expert's current testimony and previous testimony, and between the expert's testimony and published articles. In federal courts, experts must disclose the cases in which they have testified in the preceding four years and publications in the past ten years. Attorneys will use this information to obtain transcripts of prior testimony and prior publications in effort to identify inconsistencies in the expert's statements.[12]

Table 4:
Common Areas of Attack on Cross-examination

1. Lack of qualifications.
2. Prior relationship with the party, side of the case, or industry suggesting bias.
3. Amount of compensation.
4. Lack of experience when the expert is a novice witness.
5. Honesty by portraying the expert as a "hired gun" when the expert has testified a lot.
6. Inadequate assessment.
7. Poor or unreliable methodology forming the expert's opinion.
8. Inconsistencies from prior statements or publications.
9. The expert's degree of certainty.

Conclusion

Although the legal process may be unfamiliar to many psychiatrists, the psychiatrist should not feel intimidated if presented with the opportunity to serve as an expert. The psychiatric expert possesses unique knowledge and skills that can assist the court. Moreover, the psychiatrist has more expertise in matters related to mental health than the other courtroom participants. By getting familiar with the roles psychiatrists play in the courtroom and common tactics employed in the courtroom, the well-prepared psychiatrist may find it a gratifying challenge to serve as an expert witness.

Table 5:
Key Points

1. Fact witnesses and expert witnesses have different roles in the courtroom.
2. There are risks when serving in dual roles as a treating clinician and expert witness.
3. The judge determines whether the psychiatrist may be qualified to testify as an expert witness.
4. Psychiatric expert witnesses state their opinion to a reasonable degree of medical certainty.
5. Expert witnesses offer their opinions and support evidence on direct examination.
6. Opposing counsel may seek to discredit the expert and/or their opinions on cross-examination.

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Multiple-Choice Questions

41. All of the following are true of expert witnesses, *except*:

    A. They have knowledge or skill beyond the scope of the average juror.

    B. They may give opinions in court.

    C. They are typically voluntarily retained by an attorney or court.

    D. They are truly impartial.

42. Psychiatric expert witnesses should express their opinions to the following level:

    A. 100% certainty.

    B. A reasonable degree of medical certainty.

    C. Beyond a reasonable doubt.

    D. None of the above.

43. Psychiatrists testifying in court should:

    A. use professional jargon.

    B. avoid eye contact with the jury.

    C. speak in clear plain language.

    D. dismiss offers for pre-trial consultation with the retaining attorney.

44. Under the Federal Rules of Evidence, psychiatrists are qualified as expert witnesses based on the following, *except*:

    A. knowledge.

    B. skill.

    C. training.

    D. professional title.

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Best Practices in CME

Psychiatrists as Expert Witnesses

By Jennifer Piel, JD, MD; and Phillip Resnick, MD

ID#: L003374

This valuable take-home reference translates evidence-based continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Mental health professionals are commonly asked to participate in court proceedings. Not all psychiatrists feel comfortable participating in legal proceedings. This may be due, at least in part, to being unfamiliar with the legal process and one's role when serving as a witness. The role of psychiatrists as expert witnesses is discussed in this lesson. This lesson should provide guidance for testifying and help clinicians understand: (1) the circumstances calling for psychiatric expert witnesses, (2) the difference between expert and fact witnesses, and (3) the bases for expert qualification.

Key Point 1: There Are Two Types of Witnesses: Fact and Expert

Fact witnesses testify as to their direct observations. Treating psychiatrists may be called to be fact witnesses and testify to observations in the clinical relationship such as the patient's presenting complaints, diagnosis, number of appointments and medications prescribed. While serving as fact witnesses, psychiatrists do not ordinarily render opinions except under limited circumstances.

Expert witnesses, in contrast, are witnesses who testify because of their special knowledge or experience. Expert witnesses may provide opinions on issues of medical-legal significance in the case.

Key Point 2: The Trial Court Judge Determines Whether a Psychiatrist is Qualified as an Expert Witness

The judge determines whether a psychiatrist is qualified to testify. The trial court judge first considers whether the person's expertise will assist the trier of fact in the case at issue. Then, the judge determines whether the person has the appropriate specialized knowledge or other qualifications. The *Federal Rules of Evidence* (FRE) govern the admissibility of expert witness testimony in federal courts, as well as by adoption in many state courts. Under the FRE 702, a psychiatrist may be qualified as an expert on the basis of knowledge, skill, experience, training, or education.

Key Point 3: Judges Have a Gate-Keeping Role in the Admissibility of Scientific Evidence

In *Daubert v. Merrell Dow Pharmaceuticals* (1993), the United States Supreme Court identified a list of factors to guide the admissibility of scientific or technical evidence in federal courts: whether the theory or technique has been or can be reliably tested, whether it has been or can be subjected to peer review, the known or potential rate of error of the technique, the existence and

maintenance of standards controlling its operation, and the general acceptance of the technique. Trial court judges use these criteria to determine whether the scientific or technical methodology upon which expert testimony is based is sufficiently reliable. Many states also have adopted the *Daubert* approach. Other states rely on the *Frye* approach, guided by *Frye v. Unites States* (1923), which requires that the science or technique have gained general acceptance within the relevant field.

Key Point 4: Expert Opinion Testimony is Expressed to a Reasonable Degree of Medical Certainty

Although the phrasing and exact standard may vary by jurisdiction, psychiatric expert witnesses typically express their opinions to "a reasonable degree of medical certainty." In some jurisdictions, "reasonable psychiatric certainty" or "reasonable psychological certainty" is used for mental health professionals. In most jurisdictions, this means that the expert expresses an opinion that is "more likely than not" to be true.

Acute Ischemic Stroke, Post-Stroke Cognitive Deficits, and Depression

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KEY WORDS: Acute ischemic stroke • Cognitive deficits • Depression

LEARNING OBJECTIVES: This lesson will enable health professionals to: (1) define *acute ischemic stroke* (AIS) and understand its causes, (2) identify various cognitive deficits associated with AIS (3) discuss possible treatments and proactive interventions for AIS and cognitive defects, and (4) depict how depression is diagnosed and treated in post-stroke victims.

LESSON ABSTRACT: AIS occurs when there is a sudden occlusion of the arterial blood supply, followed by focal neurological deficits. More than 750,000 stroke cases occur every year in the United States alone. Strokes carry a $70 billion annual cost and have devastating effects on the quality of life of patients and caregivers alike. AIS is associated with a variety of cognitive defects and depression. The diagnosis and treatment of stroke symptoms are complicated and require immediate and expert intervention.

COMPETENCY AREAS: This lesson addresses the gap in learning in the area of knowledge, patient care, and practice-based learning and improvement in the treatment of patients with AIS and post-stroke complications, such as cognitive deficits and depression. After reading this lesson, readers will have a better understanding of AIS and how to assess and manage this dysfunction as well as post-stroke cognitive deficits/depression.

Introduction

Strokes have been voted as the second most frequent cause of death for geriatric patients, resulting in permanent disability and dementia, which contributes to an estimated 3–7% of the total healthcare costs in first-world areas. As a result, it is necessary to investigate new treatments for patients with *acute ischemic stroke* (AIS), which comprises most types of strokes.[1] **A stroke is defined as an abrupt loss of neurological functions due to vascular issues. It is categorized into ischemic (≈85%) and hemorrhagic types (≈15%).[2] Ischemia may be caused by large or small vessel occlusions, both intracranially and extracranially. Arterial occlusions result from embolic (cardioembolic and arteroembolic), atherosclerotic, traumatic, inflammatory, infectious, or degenerative mechanisms.** A spontaneous hemorrhagic stroke can result from either a parenchymal hemorrhage or atraumatic subarachnoid hemorrhage, with the latter most commonly associated with ruptured intracranial aneurysms. The least common variety of a stroke is venous infarction due to cerebral venous thrombosis.[3] Strokes have multiple possible causes and variable symptoms ranging from mild and transient to detrimental and fatal. The duration of symptoms is related to the amount of time required for vessel occlusion or how the neurovascular bed is affected by ischemia. The brain depends on adequate perfusion and oxygenation as well as metabolic waste removal for proper neurofunction, and thus ischemia leads to neuronal damage and necrosis in specific neurovascular beds.[4] AIS may lead to such severe deficits in brain function, requiring extensive treatment and rehabilitation. **The best treatment of choice predominantly depends on occlusion removal from the blood vessels, either by recombinant tissue-type plasminogen activator (rt-PA) within 0–4.5 h[5]** and/or by endovascular intervention.[6] The majority of stroke patients have at least one medical complication before and during rehabilitation. The most common complications generally include *urinary tract infection* (UTI), shoulder pain, insomnia, and other musculoskeletal pain.[7] Hence, understanding the mechanisms of AIS is an important prerequisite for diagnosis and intervention in routine clinical practice as well as clinical trials.[8]

It is important to recognize post-stroke behavioral deficits resulting from topographic lesions, including metabolic, structural, and functional connectivity abnormalities. These may be related to atypical neuronal dynamics in whole brain networks.[9]

Cognitive assessment is highly recommended after a stroke, although more research needs to be done on the applicability of basic cognitive tests. Researchers have shown that between 44% and 74% of patients had cognitive dysfunction when tested 6 months post-stroke.[10] The *Mini Mental State Examination* (MMSE)[11] and the *Montreal Cognitive Assessment Test* (MoCA)[12] seem to be the most commonly used cognitive screening tests worldwide. However, certain researchers believe that the MMSE is not sensitive enough to detect patients with mild symptoms, such as visuospatial and executive function impairments.[13] They think that the MoCA has higher sensitivity for detecting dementia than the MMSE, but is limited otherwise.[14] For example, some have determined that the MoCA does not detect common cognitive problems after a stroke, such as visuospatial neglect and apraxia.[15] Moreover, both the MMSE and MoCA screen for good verbal abilities. This means that aphasic patients can fail these tests due to language impairments rather than memory or attention problems. There is also a lack of specificity in assigning a problem to a specific cognitive function. These tests typically provide an overall score, which cannot be easily used for direct treatment targeting a specific cognitive problem.[16] *The Birmingham Cognitive Screen* (BCoS) battery is a new instrument utilized to screen individuals for cognitive problems after a stroke and to generate an expansive cognitive profile (Attention and Executive Function; Language; Memory; Number Skills; and Praxis). Most importantly, this test was designed to specifically include stroke patients and generate more diagnostic test results, such as for aphasia, by including short, high-frequency words when language is assessed indirectly and by incorporating direct response options (patients afflicted with aphasia can point at the answer without having to respond verbally).[17]

Other than cognitive dysfunction, depression is one of the most frequent neuropsychiatric disturbances in AIS, being present in 6%–52% of these patients.[18] Depression is most frequently found in left anterior (cortical or subcortical) lesions[19] or acute right hemisphere

lesions.[20] *Selective-serotonin reuptake inhibitors* (SSRIs) given to AIS patients can improve their clinical recovery as well as depression.[21] The clinical aspects and correlations of depression immediately post-stroke are less known. Most importantly, addressing the cognitive and emotional consequences of AIS is just as important as the immediate treatment of the acute symptoms of a stroke.

Etiology, History, and Prevalence of AIS, Cognitive Deficits, and Depression

Understanding the etiology, history, prevalence, and mechanisms of AIS and its sequelae is crucial for diagnostic purposes and treatment in routine clinical practice and clinical trials.[8] Moreover, a variety of techniques can be used to investigate brain function and causal relationships by correlating behavior and functional brain tasks.[22] Prior researchers have suggested that investigating thrombus composition can provide insights into the etiology of a stroke, predict intravenous thrombolysis and mechanical thrombectomy outcomes, and develop new ways to retrieve various thrombi.[23, 24] Historically, ischemia can be predominantly ascribed to small vessel disease, artery-to-artery thromboembolism (arteroemboli), cardioembolism, and occlusive arterial disease caused by atherosclerosis and arteriosclerosis. These ischemic causes are important for the prevention of secondary strokes and influence immediate treatment methods, as doctors do not have access to detailed information on the mechanisms of AIS and possible treatments of all ischemic strokes.[5]

AIS also significantly affects cognitive proficiency and functional abilities, particularly physical abilities such as speech. Decreased cognition is often correlated with decreased functional tasking post-stroke.[25] For most patients, cognitive impairment affects their functional outcomes more than their physical disabilities.[26] AIS mainly affects attention, speech/language abilities, delayed recall, executive functions, and others.[27] Cognitive impairment in the acute stroke phase is associated with the lesion location, duration, and severity, where the affected individuals with a higher degree of functional disability and more severe stroke symptoms have greater

cognitive impairment post-stroke. However, cognitive impairment in patients with less debilitating AIS symptoms has rarely been studied.[28, 29]

Cognitive screening is recommended after all strokes to guide treatment and prognosis because a stroke predisposes individuals to dementia and vice versa.[30] Brief cognitive tests are preferred because extensive batteries of tests are not practical in clinical settings.[31] Current research on short cognitive tests such as the MMSE and MoCA have been proven effective in assessing stroke damage.[31, 32] Sensory deficits or non-stroke-related problems including dominant arm disability, fatigue, and weakness are problematic in assessing cognition, but such information remains unreported in most studies.[31, 33]

Post-stroke fatigue (PSF) and *post-stroke depression* (PSD) are both common and difficult outcomes of AIS due to biomedical and psychosocial causes, as shown in Figure 1.[34] PSF and PSD are associated with one another, but do not necessarily occur together. This relationship, however, remains unclear. The question is: Does AIS cause fatigue due to depression, do AIS patients become depressed because they are fatigued, or is this a bidirectional relationship that is equally influenced by both fatigue and depression?[34] The incidence of post-stroke depression ranges between 29% and 36% and depends on the diagnostic criteria used, stroke onset, type of stroke and population, and the preferred assessment tools.[35] **Diagnosing post-stroke depression is difficult and easily missed in 50–80% of cases by clinicians with little or no psychiatric training.[36]**

There are no specific scales to measure PSF, and thus it is difficult to report its prevalence, but one study reported it ranging from 35% to 92%.[37] Another study showed that chronic fatigue could develop a couple of years post-stroke, with a prevalence of up to 40%.[38] PSF has multiple causal factors; hence, a multidisciplinary approach targeting its physical and mental aspects is necessary. One recent randomized controlled trial showed that a 12-week cognitive therapy program with graded activity training relieved PSF,[39] but more research needs to be done in this area. As for the prevalence of depression, one study found that it was 29% immediately following a stroke, while other prevalence rates were 28%, 31%, 33%, and 25% at <1 month, 1–6 months, 6–12 months, and >1 year post-stroke, respectively.[34]

Figure 1:
A Biopsychosocial Model of Fatigue and Depression Following Stroke
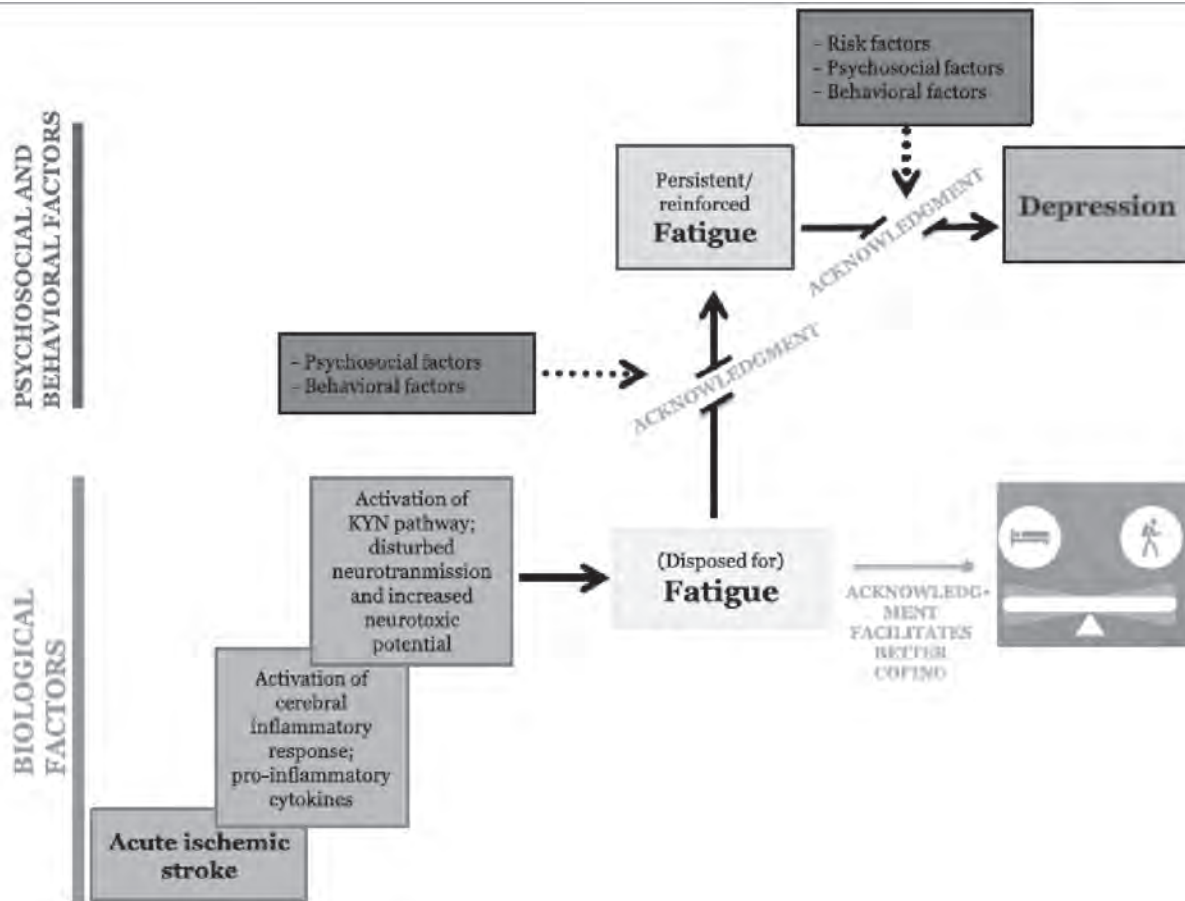
"A biopsychosocial model of fatigue and depression following a stroke. This biopsychosocial model indicates that from a biological perspective, the immune response and KYN (kynurenine) pathway activation following AIS can predict fatigue, but not (directly) depression. The acknowledgment of fatigue can facilitate the ability to cope with its symptoms, and thus possibly diminish persistent/enforced fatigue and reduce the risk of developing (clinical) depression over time. Providing stroke survivors with acknowledgment—which is a key to coping with the symptoms of post-stroke fatigue—will make it easier for them to find the correct balance between rest and activity, which in our opinion is essential to avoiding depression (used with permission)."[34]

Assessment and Diagnosis of AIS, Cognitive Deficits, and Depression

Neuroimaging is crucial as an immediate tool that can reflect strokes' pathophysiology and provide critical diagnostic information for rapid, individualized treatment.[40] Despite modern methods and techniques developed to measure strokes, the ability to measure brain function accurately and quickly in medical settings remains limited, particularly when neural injury and function contribute to overall impairment.[41] First, *functional magnetic resonance imaging* (fMRI) is the primary tool to examine network-level abnormalities caused by brain

diseases, including strokes, based on the hemodynamic response. Some post-stroke changes found by this technique include the observed lag caused by microvascular damage disrupting neurovascular coupling, the rerouting of blood flow, altered neural activity, or all of the above.[42]

MRI also provides greater spatial resolution and physiological information compared with *non-contrast computed tomography* (NCCT). *Diffusion-weighted imaging* (DWI) can detect ischemic changes within minutes of a stroke's onset. DWI allows clinicians to diagnose AIS and differentiate genuine strokes from fake ones.[43] The specific injury patterns that are identified on DWI determine the time of onset, progression, and resolution

of strokes. Following acute treatment, MRI is helpful in determining a stroke's pathogenesis because it can help visualize small strokes and the distribution of stroke lesions that may not be detected by NCCT. This is particularly true for minor ischemic strokes where the ischemic tissue volume is lower and posterior circulation strokes impair stroke visualization due to artifacts on NCCT.[40]

Electroencephalography (EEG) can be utilized to study brain function and provide insights into acute stroke symptoms. EEG metrics, such as increased slow rhythms and reduced fast rhythms, are correlated with metabolism in the brain and reflect ischemic sequelae.[44] Moreover, EEG can detect significant acute stroke effects not available from MRI.[45]

NCCT is one of the imaging modalities of choice for AIS cases because of its rapid acquisition time and availability. It can also differentiate between ischemic and hemorrhagic strokes and assess the extent of ischemic damage. A normal NCCT cannot rule out a minor stroke and has a low negative predictive value for smaller ischemic volumes. The major role of NCCT is to exclude other possible causes of acute neurological symptoms, such as brain tumors, subdural hemorrhage, or other space-occupying lesions in the case of thrombolysis contraindication.[46] For instance, long-term wedge-shaped cortical infarcts indicate possible embolism. Periventricular white matter changes or lacunes suggest small vessel disease. These findings are associated with poor clinical outcomes in those treated with intravenous thrombolysis.[47]

The *Alberta Stroke Program Early CT Score* (ASPECTS) was developed alongside NCCT to provide a reliable, reproducible grading system assessing ischemic damage in patients with anterior circulation ischemic strokes (www.aspectsinstroke.com) using a 10-point scale, where 10 pre-specified regions are observed, and 1 point is subtracted for each region with parenchymal hypoattenuation.[46] For example, lower ASPECTS scores have been linked with poor functional outcome post-therapy, whereas scores ≤7 are associated with an increased risk for thrombolysis-related parenchymal hemorrhage after intravenous thrombolysis alone or with endovascular treatment.[48]

Computed tomographic angiography (CTA) imaging is routinely used to image blood vessels. CTA is particularly crucial in AIS therapy, as well as predicting the outcome of ischemic and hemorrhagic strokes. All recently published and successful endovascular stroke trials used CTA to select individuals with proximal occlusions of their anterior circulation or collaterals.[49] Another new technology used to assess collaterals has been the multiphase CT angiogram. The multiphase CT angiogram generates images of pial arteries by triggering the first scan in the late arterial phase and acquiring two subsequent scans without additional contrast in the mid-venous and late venous phases. The multiphase CT angiogram is fast, resistant to image degradation from patient motion, has minimal additional radiation, requires no additional contrast material, provides whole-brain coverage, has no requirement for post-processing, and allows for high inter-rater reliability.[50]

Computed tomographic perfusion (CTP) estimates cerebral blood flow. During CTP, a rapid intravenous contrast bolus is given and sections of the brain are repeatedly imaged. This technique can estimate potential areas of salvageable brain tissue/ischemic penumbra.[51]

On top of the physical complications of AIS, approximately one-third of stroke survivors suffer from *post-stroke depression* (PSD) in the acute or chronic stages.[35] PSD in AIS is associated with poor patient prognosis, and thus it needs to be diagnosed and treated as early as possible.[52] Patients with PSD demonstrate more physical signs of depression rather than inward expression,[53] such as the early appearance of feeling melancholy, being in a vegetative state, and having psychological disturbance with poor social skills.[54] One study of lesion localization stated that frontal and temporal lobe area infarctions were significantly and independently associated with depression 10 days post-stroke.[52] However, some researchers observed that the hemispheric laterality of ischemic lesions was not associated with the onset of PSD in an acute post-stroke subgroup.[52, 55] Overall, there are various modalities to monitor and detect AIS symptoms and their severity.

Treatments and Treatment Issues

To treat the physical problems of AIS, intra-arterial thrombolysis in patients has had a better outcome than intravenous thrombolysis. However, some researchers have found no significant benefit of intra-arterial over

intravenous thrombolysis.[56, 57] Additionally, a mechanical thrombectomy was associated with an increased likelihood of good prognosis compared with standard alteplase treatment.[58] The neutralization of oxidative radicals is a potential therapeutic strategy because the ischemic brain is highly susceptible to oxidative damage,[59] and the prevention of these effects can be an effective measure to prevent the ischemic lesion from expanding.[60]

Although *intravenous tissue plasminogen activator* (IV-rtPA) was approved nearly 20 years ago for the treatment of AIS, only few receive it due to the narrow time window for administration, and there are several contraindications for its use. Endovascular techniques for recanalization have been developed for AIS, but there is more benefit in combining endovascular mechanical thrombectomy with IV-rtPA over IV-rtPA alone.[61] In 2015, an endovascular mechanical thrombectomy with a retrievable stent (commonly called a stent retriever), along with IV-rtPA was established as the new standard of care for AIS due to *large vessel occlusion* (LVO).[62] However, research on such neuroprotectants for AIS might be inadequate. The problems with neuroprotectant studies in rodents is that they have been tested in inbred male adolescent animals without comorbidities (such as hypertension, hyperlipidemia, or diabetes) or medications (such as anti-hypertensives, statins, or aspirin), who had eaten high-antioxidant foods, and lived in pathogen-free environments, which is in stark contrast to people suffering from strokes.[63]

Another issue with treatment is that necrosis may be present even before it can be detected via histopathology or MRI, thus diminishing the therapeutic window, which is about 1 h depending on the symptom onset. It is surprising to learn that certain clinical trials wait up to 2 days or more to intervene.[64] As a result, it is crucial to provide neuroprotective treatment for AIS patients and implement novel techniques in both research and clinical settings. Furthermore, a potential drug should have a clearly defined mechanism of action, molecular target, established toxicity, and appropriate pharmacokinetics and pharmacodynamics.[65] Only research studies with sufficient validity, *a priori* sample size calculation power of at least 80%, and adherence to reporting guidelines (such as ARRIVE) should be utilized.[66]

There are also more specific treatments such as PROACT (Prolyse in Acute Cerebral Thromboembolism Trial), which was the first *randomized controlled trial* (RCT) to investigate intra-arterial recombinant pro-urokinase (IA-proUK), and heparin that was given within 6 h of a stroke in patients with *middle cerebral artery* (MCA) occlusion,[67] but it was inadequate as a standard of care procedure.[68] *Mechanical thrombectomy* (MT) began with development of the "mechanical embolus removal in cerebral ischemia" (MERCI) device.[69]

Stent retrievers were designed for stent-assisted coiling and for retracting errant coils dislodged during endovascular techniques. These stents expand and go across the thrombus with the aid of a microcatheter. After clot removal, blood flow is immediately restored.[70] In the future, trials focusing on posterior circulation strokes are needed to determine effective treatment windows and techniques for these patients. Even though guidelines recommend using stent retrievers as the first-line device, other devices may be more useful in certain situations.[62]

As for treatment strategies for post-stroke depression and cognitive dysfunction, these include psychiatric counseling, cognitive behavioral therapy, and antidepressants. Psychiatric counseling is highly recommended for all hospitalized stroke patients. The aggressive treatment of depression and cognitive deficits early on may result in improved function and quality of life.[71] One study found that patients with at least one complication were functionally disabled at admission and discharge. Those with more severe symptoms and reduced physical and cognitive functioning upon admission had a higher rate of medical complications during rehabilitation.[7]

Finally, although alternative and complementary medicine including acupuncture is not considered a conventional therapy for post-stroke sequelae, it might have some additional positive effects on early rehabilitation. One study showed that acupuncture was deemed safe and had additional effects in improving neurologic deficits, swallowing dysfunction, cognitive impairment, and lower extremity function, but had no significant improvement for upper extremity function.[72] However, more research and better-designed acupuncture studies need to be conducted to show significant results.

Summary and Conclusions

In summary, AIS is a vast and complex disorder that is best diagnosed early and with immediate approved treatments. Stroke symptoms are diverse, but the most influential ones on overall patient wellness include cognitive deficits and depression. These need to be addressed in stroke patients to improve their quality of life and aid in better recovery. Further research needs to be done on how to promptly detect and treat AIS and its consequences. 〽

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Multiple-Choice Questions

45. What is the major cause of *acute ischemic stroke* (AIS)?

    A. Occlusion

    B. Drug overdose

    C. Age

    D. Environmental factors

46. Which one of these is *not* a cognitive deficit of AIS?

    A. Short-term memory lapses

    B. Hyperactivity

    C. Fatigue

    D. Apraxia

47. What is the best method of treating AIS?

    A. Rest

    B. Physical therapy

    C. Intravenous tissue plasminogen activator with endovascular mechanical thrombectomy

    D. Psychiatric evaluation

48. How is post-stroke depression diagnosed?

    A. fMRI

    B. *Cat scan* (CT)

    C. Psychiatric evaluation and tests

    D. *Electroencephalograph* (EEG)

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Best Practices in CME

Acute Ischemic Stroke, Post-Stroke Cognitive Deficits, and Depression

By Karen M. von Deneen, DVM, PhD; Jixin Liu, PhD;

Jie Tian, PhD; and Yi Zhang, PhD

ID#: L003375

This valuable take-home reference translates evidence-based continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to medical students, general practitioners, researchers, and family physicians who may not have up-to-date knowledge on *acute ischemic stroke* (AIS) and its medical consequences. Knowing the signs, symptoms, and sequelae of AIS can only lead to more prompt identification and improved treatment.

Key Point 1: Identification of Acute Ischemic Stroke and Its Consequences

The key to treating *acute ischemic stroke* (AIS) is by proactively identifying the signs at an early stage before they worsen. Early signs include behavioral deficits, such as sudden weakness or numbness in the face and limbs, which are usually located unilaterally. More profound signs include trouble walking, dizziness, loss of balance, lack of coordination, trouble seeing with one or both eyes, sudden confusion, struggling with speaking, and difficulty understanding others.

Key Point 2: Intervention

Immediate intervention with intravenous tissue plasminogen activator and endovascular mechanical thrombectomy prevents AIS from progressing.

Key Point 3: Competent Staff

Seeking proper personnel and well-trained staff is important in the successful treatment of AIS and its sequelae. This includes working in interdisciplinary teams at university hospitals or research facilities dedicated to studying various types of strokes and providing current intervention methods.

Key Point 4: Continuing Education

Reading current research on AIS is important to prepare for its treatment and possible prevention.

Key Point 5: Research and Development

Being involved in AIS studies will help the scientific and medical community deal with AIS directly.

Notes

Intellectual Disability Disorder (IDD): From the DSM-IV-TR to the DSM-5

Asim A. Shah, MD; Sophia Banu, MD; Roxanne McMorris, MD; and Sharadamani Anandan, MD

KEY WORDS: Intellectual Disability • DSM-IV-TR • DSM-5

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) review the new *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (DSM-5) diagnostic criteria for *intellectual disability disorder* (IDD), (2) compare changes with the fourth edition of the same manual, DSM-IV-TR, and (3) discuss the epidemiology, pathogenesis, and different treatment modalities.

LESSON ABSTRACT: IDD is a complex disorder, and the lives of individuals who have or are suspected of having intellectual disabilities are complex. This lesson reflects the changes made from the DSM-IV-TR to the DSM-5 in terms of diagnostic criteria. The most significant difference between the DSM-IV-TR and the DSM-5 is that the diagnosis is based on both the clinical assessment and standardized testing of intellectual and adaptive functions. Disentangling this intricate picture requires careful consideration. One must contemplate the interaction between the external physical and social environments, the individual's pattern of strengths and weaknesses in intellectual and adaptive functioning abilities, genetic predispositions, and any secondary behavioral characteristics (e.g., challenging behaviors, psychopathology, medical issues) from a developmental learning perspective. Individuals with IDD include a broad spectrum of levels of functioning, disabilities, and strengths.

COMPETENCY AREAS: This lesson addresses the gap in knowledge of the new DSM-5 diagnostic criteria for IDD, including an overview of the epidemiology, neurobiology, and some treatment modalities. This lesson also focuses on the neurobiology of neurodevelopmental disorders in IDD such as fetal alcohol syndrome, Down syndrome, Rett syndrome, tuberous sclerosis, and Fragile X. Two case studies are discussed outlining the assessment and treatment of IDD.

Epidemiology

In 2010, a federal statue in the United States (Public Law 111, Rosa's Law) replaced the term mental retardation with *intellectual disability* (ID). This legislation reflects a change in terminology that had already taken place in research, medical, and educational professions as well as advocacy groups. This change was reflected in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[1] because the term *mental retardation* (MR), which was used in the DSM-IV-TR,[2] is no longer in use internationally or in U.S. federal legislation.

***Intellectual disability disorder* (IDD) is one of the most common neuropsychiatric disorders in children and adolescents under age 15 years. There is a slight preponderance in boys. Approximately 30% more males are diagnosed with IDD than females.** The prevalence is estimated to be 10.37/1000 individuals. This is similar to the 1% rate based on studies conducted primarily in the US and other developed countries.[3, 4] Prevalence estimates vary by age, how ID is defined, the methods used to assess individuals, and the population under consideration.

Studies have reported the prevalence of intellectual disability to vary between 1% and 3% globally; among those, 85% have a mild intellectual disorder.[3, 4] In addition, those with moderate, severe, and profound intellectual disorders comprise about 10%, 4%, and 2% of the population, respectively.[4] Epidemiologically, a simplified classification can group subjects into Mild ID (50–70 intelligence quotient, or IQ) and Severe ID (<50 IQ).

The prevalence varies in different age groups, the highest being at school age. The time of diagnosis is also age-dependent, with more severe retardation diagnosed earlier than milder forms. Many of the persons diagnosed as having MR in childhood develop sufficiently high adaptive functional skills by adulthood that the diagnosis ceases to be appropriate.

DSM-IV-TR and DSM-5 Changes

The shift from the DSM-IV-TR to the fifth edition included many changes involving terminology and criteria. The term MR, used in the DSM-IV TR,[2] was eliminated and changed to ID. In fact, ID is the term that has been commonly used over the past 2 decades. In addition to terminology changes, we saw a shift in the criteria for certain neurodevelopment disorders. Currently, the diagnostic criteria emphasize the need for an assessment of both cognitive capacity (IQ) and adaptive functioning. Severity is determined by adaptive functioning rather than IQ score.

In the DSM-IV-TR,[2] MR is defined on the basis of three essential features: (1) subnormal intellectual functioning, which is characterized by an IQ lower than 70, based in most cases on the administration of an appropriate standardized assessment of intelligence; (2) commensurate deficits in adaptive functioning and adaptive skills, which involve one's social and personal sufficiency and independence, which are generally measured on instruments such as the *Vineland Adaptive Behavior Scales* or a similar scale. The final criterion is (3) onset before 18 years.

In the DSM-IV-TR the degree of severity was based exclusively on the individual's level of intellectual functioning, which was determined by IQ.[2] Mild MR (as it was previously called): IQ 50–55 to approximately 70; Moderate MR: IQ level 35–40 to 50–55, Severe MR: IQ level 20–25 to 35–40; and Profound MR: IQ level below 25. In addition to the varying degrees of disability, there is a category that does not have a particular subtype—MR, Severity Unspecified—when there is a strong presumption of MR but the person's intelligence is untestable by standard tests. In contrast, in the DSM-5,[1] there is greater recognition of the importance of clinical judgment in diagnosing an intellectual disability. This change in the DSM-5 reflects the current understanding that intelligence is not a uniform concept and that an IQ score does not always provide a valid measure of how a person navigates the demands of daily living.

In the DSM-5, there are no longer subtypes of intellectual disability (i.e., mild, moderate, severe, profound) relating to IQ/scoring on a test. Instead, the subtypes reflect the severity of affectedness (i.e., mild, moderate, severe, profound). The criteria for establishing the severity of affectedness in the DSM-5 focus on the ability to cope with the stresses of the environment and creating levels of personal independence and social responsibility based on age, sociocultural background, and community setting.[1]

The DSM-5 offers descriptions of severity for three domains of adaptive functioning: conceptual, social, and practical.[1] Conceptual refers to language, reading, writing, math, reasoning, knowledge, and memory; social, as in empathy, social judgment, interpersonal communication skills, and the ability to follow rules and to make and retain friendships; and practical, or self-management in areas such as personal care, job responsibilities, money management, recreation, and organizing school and work tasks.

ID is the result of a complex clinical picture. In addition to the features essential to a diagnosis of ID, many problems and behavioral characteristics are common in individuals with intellectual disabilities. Often, these characteristics may hinder the process of assessing the individual's overall intellectual and adaptive functioning to determine the appropriateness of the diagnosis.[5] In situations in which an individual demonstrates differing levels of severity across the various domains, the clinician is to assign the level that best fits the individual on average. The inclusion of this severity guide for the clinician acknowledges that many individuals with an intellectual disability demonstrate a pattern of strengths and weaknesses across domains of functioning.

Neurobiology of IDD

IDD is a common neurodevelopmental disorder and is defined as an IQ <70 with 2 or more disorders of adaptive behavior with childhood onset, which include activities of daily living, communications skills, and social skills. Many of the ID brain architectures are due to impaired synaptic plasticity.

In addition to the simplified classification of Mild and Moderate IDD, IDD can also be categorized as Syndromic and Non syndromic based on the presence or absence of additional phenotypical features. Some of the common causes of IDD are Down syndrome, Rett syndrome Fragile X, thyroid hormone deficiency, toxins like lead, and fetal alcohol syndrome. More than 60% of children with autism have an IQ <70.

In more than 60% of the cases, the cause is unknown/multifactorial. For the rest of the intellectually disabled population, (25%–50%) a genetic cause is most common.[6]

Fetal Alcohol Syndrome:

Fetal alcohol syndrome is characterized by specific facial anomalies, neuronal cell loss in the brain, functional and structural loss in the brain, significant growth retardation, and learning difficulties. Ethanol interacts with glutamate (excitatory) and GABA (inhibitory) neurotransmitters in an unfavorable manner that results in disrupting neuronal function and architecture, hindering both pre- and post-natal growth. Powerful excitatory neurotransmitters are required for learning and memory. This is, in turn, dependent upon plasticity, which is directly dependent upon a balance between inhibitory and excitatory neurotransmission.

- **Ethanol enhances GABA-nergic inhibition and blocks NMDA-mediated trophic effects**

- **The blocking of NMDA-mediated trophic effects causes apoptosis and abnormal migration in the fetal brain**

Purportedly, the blood-brain barrier prevents this extraneous glutamate from entering the brain. Glutamate has been identified to act at 4 major types of receptor sites in the brain:

1. **NMDA**

2. **AMPA**

3. **Kainate**

4. **Metabotropic**

Syngap-1 is one of the commonly observed proteins in all four receptor sites. This protein normally represses synaptic excitability during development. Enhanced synaptic excitability (due to Syngap-1 mutation) causes the premature development of dendritic spines, causing growth retardation and impairing intellectual growth.

Neuroligin-1 is another important component of the 4-NMDA receptor sites, providing negative feedback to the presynaptic terminal, reducing the excitatory neurotransmission, and mutations of this molecule are implicated in autism and neurobehavioral disturbances.

Normally, changes in the 4 GABA receptors occur with plasticity due to excitation and are important for long-term potentiation and memory and growth.

Mutations in the proteins of these receptors can lead to long-term depression and the development of Alzheimer's disease, as occurs in Down syndrome.

Down Syndrome—Trisomy 21:

Also known as trisomy 21, this is a condition where individuals have 47 chromosomes in each cell instead of 46. Trisomy 21 is caused by an error in cell division called nondisjunction, which leaves a sperm or egg cell with an extra copy of chromosome 21 before or at conception.

There are specific neuron abnormalities seen in this condition, which include:

- **Shorter, thinner dendritic spines.**

- **Cholinergic neuron atrophy—in the nucleus Basalis of Meynert.**

- **Reduced retrograde transport of *nerve growth factor* (NGF) into the nucleus Basalis of Meynert.**

- **Increased GABA-nergic inhibition.**

- **During normal development, the dendrites exhibit an increased number of shorter spines; in Down syndrome, there are shorter and thinner spines.**

Rett Syndrome:

Rett syndrome is a rare, but severe brain disorder that affects mostly girls. Rare exceptions can be seen in men also. It is usually discovered in the first 2 years of life and can be very debilitating.

Its features include:

- **Wringing or patting hand movements.**

- **MECP2 gene mutations, along with BDNF growth factors result in the excitotoxic death of neurons as well as decreased synaptic connections.**

- **Elevated levels of glutamate found in the CSF.**

Fragile X Syndrome:

Fragile X syndrome is a genetic condition that causes learning disabilities and cognitive impairment. It affects males more severely than females, and affected individuals usually have delayed development of speech and language by age 2.

- **10% of all inherited cause of IDD have Fragile X syndrome.**

- **One in 1,500 boys and 1 in 2,500 girls are affected.**

- **The characterized phenotype includes MR, ADHD, autism, long ears, large testicles, and characteristic facies.**

- **Long dendritic spines that are tortuous.**

- ***Long-term depression* (LTD), as explained above, is the hallmark feature of neuronal injury, which results in significant spine volume loss.**

- **LTD is mainly due to reduced AMPA activity.**

- **Medications such as Ampakine compound to help in the positive modulation of the AMPA –glutamate receptor.**

- **mGlur5 receptor antagonists reverse neuronal changes.**

- **Baclofen has decreased the presynaptic release of glutamate by activating the GABA-B receptors.**

Tuberous Sclerosis:

- **Characteristic features include IDD, infantile spasms, seizures, and heart and kidney tumors.**

- **Hamartin/Tuberin aberration—described as a causative factor.**

- **Treatment with Rapamycin helps with the treatment of seizures.[7]**

Case Study 1

The patient is a 16-year-old single male, living at home with his parents and 3 other siblings—a 17-year-old sister and 20-year-old brother who are both disabled, and a younger 15-year-old brother. He has diagnoses of severe IDD, Fragile X, and ADHD. The patient has severe language impairments, severe cognitive-linguistic deficits,

severe articulation impairments, and severe pragmatic language impairments secondary to Fragile X syndrome.

He has been in our clinic since 2003 and has been compliant with medications and follow-up care. His current medications include:

- **Focalin XR 10 mg po qam**

- **Clonidine 0.1 mg po qhs**

- **Supportive therapy provided to the mother and patient at every visit**

Functioning: He has primarily been under the care of his mother, who brings him to all his appointments and provides his entire history. She is the one who gives him his medications, takes care of his basic needs, prepares his meals, makes sure he is taking care of his hygiene, puts him on the bus to school, and picks him up, as he is unable to go anywhere by himself. The patient is able to eat by himself, use the restroom, and put his clothes on and take them off. He attends a life skills classroom in a public school, where he receives special education, and he has been compliant with teachers and follows through on directions in school.

Course of Treatment: At the beginning of his treatment here in our child clinic, there were some reported incidences of mild aggression and temper tantrums at home and school when he did not get his way, which seemed to have calmed down as he grew older. In fact, in the past 6 years, his mother has reported only one incident of him being oppositional toward his teacher (this incident was related to a smart phone that he had taken to school).

His medications initially were *risperidone* (Risperdal) and *dexmethylphenidate HCL* (Focalin XR) for a number of years. Over time, risperidone was decreased and tapered off, and *clonidine* (Catapres, Kapvay) was added; Focalin XR was continued. He has not had any problems with the medications and has been stable psychiatrically over the last few years.

Labs: Normal, including his lipid profile and HbA1C.

MSE: Alert and oriented to place and person only, young male, overweight, large ears, dressed casually, fair hygiene, wearing dark glasses, which he takes off and puts back on during the session.

Limited eye contact, cooperative with the interview.

Normal gait, no psychomotor retardation or agitation.

Speech: Abnormal, severe articulation problems, dysarthria, decreased volume, attempts to repeat words, mostly "Nooooh" and "Yaah" in a long, drawn-out fashion, nodding his head trying to answer questions asked, smiling, and a bit shy at times.

Thought process: Unable to assess.
Though content: Unable to assess.
Insight and judgment: Poor to fair/poor to fair.
Impulse control: Fair.

Case Study 2

The patient is a 35-year-old single Hispanic female, unemployed, living with her parents, carrying a diagnosis of tuberous sclerosis, a mood disorder with major depressive-like episodes secondary to her medical condition, and moderate IDD.

The patient is currently stable on her current medications. Psychiatric medications include:

- *Quetiapine XR* **(Seroquel) 100 mg at bedtime**

- *Fluoxetine* **(Prozac and Sarafem) 80 mg at bedtime**

- **Supportive therapy provided to the mother and patient at every visit**

- *Metformin* **(Glumetza, Glucophage) 500 mg twice a day**

- *Terbinafine* **(Lamisil, Terbinex) 250 mg tablet daily**

- *Lipase-protease-amylase* **(Creon) 12,000–38,000–60,000 units thrice a day**

- *Primidone* **(Mysoline) 250 mg tablet four times a day**

Course of Treatment: The patient has been following up in our clinic since 2005 for her mental health concerns and has been seeing a neurologist and primary care physician at another facility for her neurological condition. Her last seizure was in November of 2011.

Initially in 2005, the patient presented to our clinic with episodes of agitation precipitated by not getting her

way, during which she would throw things, hitting others including her mother; she was "nervous and anxious," as described by her mother, "upset every day," having crying spells, and had a depressed mood "desperada."

She was on quetiapine 150 mg in the mornings and 200 mg at bedtime and fluoxetine 60 mg daily. The patient calmed down and had fewer episodes as the years went by. She continued to have weight gain and somnolence side effects, but her labs, including her lipid profile, were normal. Quetiapine was decreased to 150 mg in the am and 100 mg at night as she continued to improve.

In 2011, Quetiapine was switched to the XR form, as her mother reported that the patient was getting anxious and upset every day; after the switch, the patient's "desperada" decreased to 3 times per week. She was now getting quetiapine XR 100 mg twice a day and fluoxetine 60 mg daily,

She started listening to the radio, watching movies (her favorite movie was "The Lion King"), taking showers every day, riding her bike, and going for walks. She responded to psychoeducation about healthy eating and stopped drinking soda.

Quetiapine XR was further decreased to 50 mg in the am and 100 mg at bedtime in 2013 and then to 100 mg at bedtime in 2014. She did not have any periods of agitation or nervousness and anxiety; however, she expressed feeling lonely and wanting to get married and "be like other people." The patient had complained of depressive symptoms at that time. Her mother had been advised to get the patient into a day program to attend groups for her to meet others, but she would refuse to go, and family was unable to convince her.

Functioning: The patient was able to take showers daily, change her clothes, feed herself, ride a bike, ask for directions, read 1st-grade level books, write, and speak in Spanish and English.

Social history: The patient lives with her parents. Her father works and her mother stays at home and takes care of her. She has other siblings who are married and live separately; they meet regularly for meals and get together as a family.

Labs: In 2014, her lipid profile was normal, her HbA1c was 6.3, and her most recent HbA1C from Sept 2015 was 6.9. Her PCP started her on Metformin 500 mg twice a day in 2015. Fluoxetine was increased to 80 mg daily to help with her depressive symptoms

toward the end of 2014. The patient did well, was able to express herself more effectively, did not have any depressive symptoms, lost weight, continued making healthy choices, continued to ride her bike, and her BMI went down from 40 to 32.99 in the past 1 year.

MSE: Alert and oriented to place, person, and time.

Appearance: Fairly groomed, appears younger than stated age, casual attire, multiple chronic papules on her nose and nasolabial area.

Behavior: Pleasant and cooperative, childlike in her interactions.

Motor: Good eye contact; no psychomotor retardation or agitation.

Speech: Fluent and spontaneous, not pressured, normal volume.

Mood: "Fine."

Affect: Euthymic, childlike; laughs nervously at times, which is not volitional, appropriate to content.

Thought content: No suicidal ideation; no homicidal ideation; no delusions.

Thought process: Logical and goal directed at times; perseverating at times, flight of ideas at times but could be redirected; no loosening of associations.

Insight/Judgment: Fair/fair.

Perceptions: No auditory or visual hallucinations.

Available Treatments

Most of the available treatments are directed toward the optimization of functioning through *individualized education plans* (IEPs). Since few available treatments are FDA approved, many options are off label, investigational, and novel.

- **Biological treatment: Dietary restriction in** *PhenylKetonuria* **([PKU]; if untreated child can develop IQ as low as 30. Newborn screening for PKU, Hurler's syndrome has helped address this. BH4 (phenylalanine hydroxylase cofactor) has helped to improve symptoms of PKU.**

- **Prenatal: Avoiding alcohol, the treatment of hypothyroidism in the mother, avoiding lead exposure.**

- **Stem cell therapy with newborn screening: Hurler's disease.**

- **Enzyme replacement therapy: Demonstrates improved cognition in Pompe disease.**

- **Fragile X: FMRP directly responsible for dendritic growth through the GABA-nergic system.**

- **Decreased FMRP results in the uncontrolled activation of mGlur5 activation, which results in aberrant dendritic growth: Initial results with Arbaclofen have shown improvement in social functioning and behavior. mGluR5 antagonists: "Fenobam" has shown efficacy.**

Rett Syndrome:

Below, the treatment focus is more symptomatic improvement.

- **Mutations in the MeCP2 gene.**

- **MeCP2 is responsible for neural homeostasis regulation and synaprogenesis.**

- **BDNF (trophic factor) ameliorates the deficit.**

- **Insulin-like growth factor is similar in effect and crosses the blood-brain barrier.**

- **Trisomy 21 –Vitamin E has been proven to have some utility for Alzheimer disease.**

  - **Memantine – A glutamine antagonist.**

  - **DYRK1A – Overexpressed in Down syndrome – Epigallocatechin gallate modulates this gene; DYRK1A is associated with neurofibrillary tangles and splicing regulation.**

  - **Lithium and baclofen have shown some utility in mouse models.**

Treatment of Comorbidities

IDD presents not only as a primary DSM-V diagnosis, but patients also suffer from numerous comorbidities, such as depression, anxiety, mood swings, lack of concentration, and even psychotic symptoms. Comorbid disorders are also treated based on presenting symptoms, which can differ in each patient. The treatment considerations include:

- **SSRIs, such as fluoxetine, to treat depressive symptoms.[8]**

- **Anticonvulsants/mood stabilizers, such as valproic acid, carbamazepine, and lithium, have been found to be effective for affective symptoms and aggression.[9, 10]**

- **Atypical antipsychotics, such as risperidone and ariprapazole.[10, 11]**

- **Stimulants for ADHD, such as methylphenidate.**

- **Alpha-adrenergic agonists.[10]**

Newer Treatments Include:

- **Micro RNA – NON-coding RNAs that bind to mRNA and regulate their translation.**

- **Stem cell therapies – Evidence has not been sufficient, although there are some promising animal studies.**

- **Histone deacytelase inhibitors (HDAC inhibitors).**

  - **Histone acetylation is involved in learning and memory.**

  - **ID disorders – Fragile X, etc. show decreased histone acetylation.**

  - **HDAC inhibitors have shown utility in protecting against cerebral ischemic damage.**

  - **HDAC inhibitors enhance angiogenesis, neurogenesis, and neuronal migration.**

Carbon monoxide has a similar effect.

- **Gentamicin for disorders due to mutations resulting in premature stop codons, cystic fibrosis, and Duchenne muscular dystrophy.**

- **Brain stimulation – Both TMS and DBS have been used to treat ID disorders.[7, 12]**

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Multiple-Choice Questions

49. **Which is one of the most common neuropsychiatric disorders in children and adolescents under the age of 15 years?**

    A. Rett syndrome

    B. IDD

    C. Bipolar disorder

    D. Down syndrome

50. **Which of the following is correct about Fragile X syndrome?**

    A. It comprises 10% of all inherited causes of IDD.

    B. This syndrome affects 1 in 1,500 boys, and 1 in 2,500 girls.

    C. The characterized phenotype includes mental retardation, ADHD, autism, long ears, large testicles, and characteristic facies.

    D. All of the above.

51. **Regarding IDD, the DSM-5:**

    A. has degrees of severity based exclusively on the individual's level of intellectual functioning, which is determined by IQ.

    B. offers descriptions of severity for three domains of adaptive functioning.

    C. has no recognition of the importance of clinical judgment in diagnosing intellectual disability.

    D. has subtypes, namely mild, moderate, and severe.

52. **Fetal alcohol syndrome is characterized by:**

    A. specific facial anomalies.

    B. neuronal cell loss in the brain, functional and structural loss in the brain.

    C. significant growth retardation and learning difficulties.

    D. All of the above.

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Best Practices in CME

Intellectual Disability Disorder (IDD): From the DSM-IV-TR to the DSM-5

By Asim A. Shah, MD; Sophia Banu, MD; Sharadamani Anandan, MD; and Roxanne McMorris, MD

ID#: L003376

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

This lesson addresses the gap in knowledge of the new DSM-5 diagnostic criteria for *intellectual disability disorder* (IDD), including an overview of the epidemiology, neurobiology, and some treatment modalities. This lesson also focuses on the neurobiology of neurodevelopmental disorders in IDD.

Key Point 1: Functional Disability and Medical Care Costs

Patients with IDD have higher medical care utilization and greater functional disability than other psychiatric patients. This lesson will make clinicians feel more equipped to deal with this often challenging patient population.

Key Point 2: Changes in the DSM-5

The most significant difference between the DSM-IV-TR and the DSM-5 is that the diagnosis is based on both the clinical assessment and standardized testing of intellectual and adaptive functions. The DSM-5 offers descriptions of severity for three domains of adaptive functioning.

Key Point 3: No FDA-Approved Medications

There are no FDA-approved medications for IDD. Nonetheless, symptomatic treatment is available for different and varying symptoms, although none may be fully effective.

Key Point 4: Multi-Disciplinary Approach is Needed to Treat IDD

Effective treatment of IDD require a multi-disciplinary approach with medications and behavior management, and even with both approaches, complete relief is difficult.

Notes

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Attention-Deficit Hyperactivity Disorder: Overview and DSM-5 Changes

Ayesha Mian, MD; Sana Younus, MBBS; and Asim A. Shah, MD

KEY WORDS: *Attention-Deficit Hyperactivity Disorder* (ADHD) • DSM-5 • Stimulant

LEARNING OBJECTIVES: Upon reading this lesson, clinicians will: (1) review the history of *Attention-deficit hyperactivity disorder* (ADHD); (2) appreciate the prevalence of ADHD; (3) distinguish the differences between the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) and DSM-5 diagnostic criteria for ADHD; (4) consider how ADHD presents in adult and childhood case studies; and (5) review the available treatment options for ADHD.

LESSON ABSTRACT: ADHD was first defined in modern literature in the 19th century and has changed names and diagnostic criterion from minimal brain damage to the current form of ADHD in the DSM-5. While the DSM-5 increased the minimal age at which ADHD can be diagnosed to 12 years, several other modifications in the criteria are listed in this lesson as well. Since it is difficult to diagnose ADHD in adults, we have included one case each for children and adults to make it easy for our readers to understand for diagnostic purposes. Lastly, treatment options are also discussed.

COMPETENCY AREAS: This lesson will allow clinicians to employ evidence-based diagnostic practice in their treatment of ADHD and use the treatment options discussed. Furthermore, since the diagnosis of adult ADHD is always a difficult one, a case example is used to explain it better.

Introduction

Difficulties with attention, hyperactivity, and impulsivity are commonly seen in individuals worldwide, particularly in children and adolescents, and usually represent normal developmental benchmarks. A diagnosis of *attention-deficit hyperactivity disorder* (ADHD) is made when a cluster of symptoms with a specific course and specific changes in neuropsychological and neurobiological functioning are present in multiple settings. These symptoms cause a disruption in general functioning; they often have a genetic component and include the presence of certain risk factors. ADHD is one of the most common mental disorders in children and adolescents under 18 years of age, with a prevalence of 5% in this population.[1]

ADHD was first defined in the medical literature in the nineteenth century by Heinrich Hoffmann, a German psychiatrist, who described children with hyperactivity and impulsivity in a children's book "Slovenly Peter" and named this condition "impulsive insanity" or "defective inhibition."[2, 3] Later, Dr. George Still highlighted the presence of similar symptoms in children and attributed them to a "deficit of moral control." This gave rise to the stigma that children with ADHD are *purposefully* behaving a certain way and are responsible for their behavior.[2, 3] Subsequent research pointed to the biological basis of the condition and associated the disorder with brain lesions. The disorder was then named *minimal brain damage.*[4] Soon after, it was found that brain lesions are not present in all patients, and the disorder was renamed *"minimal brain dysfunction."*[5]

The World Health Organization's *International Classification of Diseases* (ICD) included the disorder in its 9th edition and named it a *hyperkinetic syndrome of childhood,* focusing on the symptom of hyperactivity; this was later changed to *hyperkinetic disorder* in ICD 10.[6] The American Psychiatric Association recognized the disorder in the second edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-11) and labeled it a *hyperkinetic reaction of childhood.* In the 1980s, more emphasis was laid on inattention as an integral part of the disorder, which led to the new term attention deficit disorder with or without hyperactivity in the 3rd edition of the DSM, and this was subsequently changed to ADHD in the DSM editions that followed.[7]

The prevalence of ADHD varies with the type of criteria used, but a recent systematic review of 102 studies from all over the world estimated the prevalence to be 5% for individuals under the age of 18 years.[1] **The prevalence is greater in males than in females; the male to female ratio is about 3:1 in epidemiological data and up to 9:1 in mental health clinic samples.[8]**

Diagnosis and DSM-5 Criteria

A cluster of symptoms demonstrating inattention, hyperactivity, and/or impulsivity primarily characterizes ADHD. The symptoms should begin in early childhood and must differ in presentation or intensity from what is expected in normally developing children. The symptoms must present in at least two settings (e.g., school, home, work). It is important to know that symptoms may differ in appearance depending on the given setting. Signs may be minimal in a highly structured environment, or when a child is getting rewards for appropriate behavior, is under close supervision, is in a new setting, has external stimulation (e.g., electronic screens), or is engaged in activities of the child's interest.

There are three subtypes of ADHD: (1) *combined presentation*: when symptoms of inattention and hyperactivity are both present in an individual, (2) *predominantly inattentive presentation*: if only symptoms of inattention are present, and (3) *predominantly hyperactive/impulsive presentation*: if symptoms of hyperactivity and impulsivity are primarily present. The symptoms have to be present for the last 6 months to make one of the above diagnoses.

The criteria for inattention include symptoms like distractibility, forgetfulness, losing daily necessities or losing track of objects, reluctance toward tasks that require mental effort, disorganization, difficulty sustaining attention, difficulty following through with instructions, making careless mistakes, and not listening when spoken to. In adolescents and adults, it is common to observe that patients often underestimate time in relation to tasks to be executed and tend to procrastinate.

Hyperactivity is characterized by excessive physical activity that is unexplained by age and normal development, constant feelings of restlessness, making patients incapable of remaining still even in situations

in which that is expected, purposeless motor activity that affects the environment in a negative way (frequently standing up and walking purposelessly when they should remain seated, or moving their hands and manipulating small objects when they are expected to remain still). These children are often unable to play quietly, frequently squirm or fidget, may talk too much, or run around aimlessly. Terms like constantly "on the go" or "as if driven by a motor" are often used to describe these children.

Impulsivity is often manifested as difficulty waiting for their turn, blurting out answers out of turn or before the question is finished, acting without thinking, interrupting others with disregard for the consequences, and a need for immediate gratification. Impulsive children have difficulty delaying an action or response even when they know that the action will have negative consequences.

The severity of these subtypes can also be marked as mild, moderate, or severe, depending upon the impairment in social and occupational functioning. If the patient was diagnosed with ADHD but does not have sufficient symptoms to meet the criteria at present, he or she can be considered in partial remission. It is important to note that the exclusion criteria do not include *autism spectrum disorder* (ASD) in the DSM-5; hence, ADHD and ASD can be diagnosed in the same individual. When all criteria for ADHD are not met, the individual can be diagnosed with either "other specified ADHD" or "unspecified ADHD." If the clinician describes the reason for not meeting the criteria, other specified ADHD can be used, e.g., "other specified ADHD with insufficient inattention symptoms." If the reason is not described, then the latter diagnosis of "unspecified ADHD" may be used.[9]

There have not been significant changes to the diagnostic construct of ADHD in the DSM-5—the 18 core symptoms remain the same. Changes include the age of onset, symptom threshold for adults, and the removal of ASD from the exclusion criteria. Less significant changes include modifications to the ADHD subtypes and the inclusion of more developmentally appropriate examples for the 18 core symptoms.

Keeping in mind the neurobiological basis of the disorder, it is now a part of "Neurodevelopmental Disorders" instead of the chapter "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence." The symptoms of inattention and hyperactivity-impulsivity broadly remain the same, although examples are added to each symptom, which can be used while interviewing the caregivers. Six symptoms are required to diagnose ADHD in children, for either inattention or hyperactivity-impulsivity, although for older adolescents and adults (over 17 years' age), five symptoms from either of the two domains are enough to warrant a diagnosis. Several symptoms need to present and cause significant functional impairment before the age of 12 years to diagnose an individual with ADHD. The age criterion has also changed from 7 years in the DSM-IV to 12 years in the DSM-5.[9]

Differences in Presentation

Depending on the subtype of ADHD, its presentation can vary from child to child. As stated above, inattention usually presents as the inability to sustain focus, being disorganized, wandering off, and lacking persistence, which is not due to defiance or a lack of comprehension. The predominantly inattentive type is more common in girls and is commonly associated with poor academic performance, cognitive deficits, and delayed development. It is seen less commonly in clinical settings and presents more commonly in middle and high school age children.

Hyperactivity refers to inappropriate restlessness, fidgetiness, and excessive motor activity. It decreases as the child grows older. Children with predominantly hyperactivity symptoms of ADHD present to clinical settings because they are more disruptive at home and school.

Impulsivity, as stated earlier, presents as difficulty in delaying gratification, making hasty decisions with no concern for the consequences, and interrupting conversations. The predominantly hyperactive-impulsive type is less common in both clinical and community settings and is more commonly seen in preschoolers.

The combined subtype is the most commonly diagnosed subtype in clinic settings and has the strongest association with *oppositional defiant disorder* (ODD). It is also associated with greater functional impairment, making treatment quite challenging. The combined subtype

has been more frequently seen in elementary school age children.

Evaluation of all three core symptoms (inattention, hyperactivity, and impulsivity) is particularly difficult among preschoolers, as these behaviors are normally present in this age group; a diagnosis of ADHD may only be made if the symptoms are very severe, persistent, pervasive, and significantly impair functioning in the child's environmental context. During the school years, symptoms come into focus based on poor academic functioning and difficulties in social interaction with peers and adults due to impulsive behaviors. Adolescents present with a lack of focus, restlessness, poor decision making, lack of self-control, and at times reckless risk taking. They are more prone to early pregnancies, substance abuse, and truant behaviors than age-matched teenagers without ADHD.

ADHD is a chronic disorder and often persists in adulthood, although some variation is seen across studies, ranging from 15% (presence of the full syndrome) to 40%–60% (with partial remission).[10, 11] Like normal children, children with ADHD develop better impulse control, executive function, and ability to remain calm as they mature, although they do so at a slower pace than their peers. Persistency also depends on the severity of illness, and patients with more severe illness and a combined-type presentation are at a higher risk of persistence into adulthood.[12, 13] Symptoms of adult ADHD are more heterogeneous and can include inattention, distractibility, disorganization, and the failure to complete tasks. Hyperactivity fades away with age, and adults may just have an inner feeling of restlessness. Symptoms in adult life are also associated with negative outcomes, such as lower academic achievement, marital problems and dissatisfaction, divorce, difficulty dealing with offspring, lower job performance, unemployment, maintaining job positions below the individual's potential, involvement in traffic accidents, and increased risk for other psychiatric disorders, like substance abuse and depression.[14–17]

Risk Factors

ADHD is a multifactorial disorder with a strong genetic component that does not follow the Mendelian patterns of inheritance. Data from twin and adoption studies have yielded a heritability of 75%. Environmental factors also play an important role.

Many candidate genes have been associated with ADHD, but no one single gene causes the disorder, as each one adds a small risk to the occurrence of the disorder. These genes are related to the catecholamine systems in particular.[18–21] Genome-wide studies have failed to identify new polymorphisms as a cause of this disorder. This has led researchers to evaluate other hypotheses regarding its etiology. One such hypothesis is the interaction between genes and the environment, which is currently under study.[22]

Environmental Risk Factors:

Among environmental risk factors, prematurity is considered an important one.[23] Some evidence points toward low birth weight and intra-uterine exposure to tobacco as probable risk factors.[24–26] Other factors that require more evidence include intra-utero exposure to alcohol and drugs, peri and prenatal complications, traumatic brain injury, psychological problems during pregnancy, and early deprivation.[27-29] No conclusive data exist to establish food additives and environmental toxins as causes.

Neurobiological and Neuroimaging Changes:

Recent data suggest the presence of significant brain changes in patients with ADHD. It must be made clear that this does not mean *brain dysfunction,* and a causal relationship between these changes and the disorder is not yet established. **The most consistent structural brain imaging findings in children with ADHD include significantly smaller volumes in the dorsolateral prefrontal cortex, caudate, pallidum, corpus callosum, and cerebellum.** Data support the presence of frontal-striatal dysfunction in patients with ADHD. Deficits in executive function and inhibitory control are present in these individuals, which are associated with thalamocortico-striatal pathways.[30] The major neurotransmitters involved in these areas are GABA and catecholamine.[31] Research points toward a dysregulation in catecholamine transmission.[32] These are confirmed by newer brain imaging techniques like SPECT, PET, fMRI, and PMRS. Most studies have found abnormalities in cerebral activation in ADHD with a hypoperfusion of the frontal and striatal areas. Brain imaging done while

individuals were performing a task that challenges the inhibitory control of the brain also showed defects in activation of those areas of brain involved in inhibition, i.e., the frontal and striatal regions. This is also confirmed by the fact that the medications used to treat ADHD are dopamine and norepinephrine agonists. A delay in cortical maturation is also seen in patients with ADHD, especially in the lateral pre-frontal cortex, an area associated with inattention.[33]

Treatment of ADHD

The treatment of ADHD is multimodal, as the disorder affects multiple domains of life and may affect behaviors at school, home, and social situations as well as academic performance. An individual treatment program should be designed for each child depending upon his or her needs. As ADHD has a strong biological component, pharmacotherapy plays a very important role. The decision to use pharmacotherapy and its dosage is based on the age of the child, severity of the illness, side effects of the medication, comorbid medical conditions, adherence issues, and the availability and cost of medications.

Pharmacological Treatment of ADHD:

Stimulants are the first-line treatment for ADHD. There is extensive evidence of their efficacy for the core symptoms of ADHD, namely hyperactivity, inattention, and impulsivity.[34] Double-blind placebo-controlled trials showed clinical response in 65%–75% of patients, both adults and children, compared to 4–30% for the placebo. The effect size is also shown to be greater than the placebo, which varies from 0.8 to 1.1, one of the largest effect sizes of any psychotropic medication.[35]

Methylphenidates (Ritalin, Concerta) and amphetamines are the two types of stimulants, which are available in various formulations. These are available as short-acting, long-acting, and sustained-release formulations and have the same efficacy.

Based on the standard of care, a short-acting stimulant should be started at a small dose and titrated to a dose that has the maximum benefits and minimum side effects. Based on the need for symptom control during the day, short-acting stimulants may be replaced by intermediate or long-acting stimulants for the ease of dosing. The common side effects of stimulants include

insomnia, headaches, irritability, restlessness, agitation, tremors, a loss of appetite, nausea, and weight loss. These side effects tend to be mild, dose-dependent, and transitory.[36] Stimulants may also exacerbate tics, psychotic and manic symptoms, and seizures; hence, stimulants should be used with caution in individuals with these disorders, and other options should be considered as an alternative. There has been a concern about the risk of sudden cardiac death and stroke with the use of stimulants. Multiple studies and meta-analyses have failed to show an increased risk of serious cardiovascular events. Although the risk cannot be completely ruled out, the absolute magnitude of such a risk is very low.[37–42] Stimulants are also shown to slightly reduce growth in some children, which may concern many parents. Growth needs to be monitored while children are being treated with stimulants. Taking drug holidays during school breaks can minimize the risk. Other options include reducing the dose or switching to *atomoxetine* (Strattera).[43] All stimulants have the potential for abuse. Many studies have shown that individuals with ADHD have a greater prevalence of substance abuse disorder, although stimulants are not shown to increase the substance abuse in these individuals.[44–46] In cases of contraindications, treatment failure, or intolerance, second-line agents may be used. These include atomoxetine, *guanfacine* (Intuniv approved for ADHD in 2013), and *clonidine* (Kapvay approved for ADHD in 2010).[47] Atomoxetine is a selective noradrenergic reuptake inhibitor that is superior to placebos and has an effect size higher than that of other non-stimulant medications, but smaller than that of stimulants.[48] It can be given once or twice daily and may have less pronounced effects on appetite and sleep than stimulants. Atomoxetine can reduce anxiety and can be used in individuals with comorbid anxiety disorders. It can also be used in patients with a history of substance abuse when the use of stimulants is not preferred. It has a slower onset of action and hence should be used at a therapeutic dose for at least a few weeks to obtain its full effect. Common side effects of atomoxetine include gastrointestinal symptoms and increased heart rate and blood pressure.[36] Clonidine and guanfacine are α2 agonists, which have shown efficacy in the treatment of hyperactive/impulsive symptoms of ADHD. These can also be used for comorbid aggressions or to alleviate the

side effects of insomnia and tics. Guanfacine is more selective than clonidine and has fewer side effects like somnolence. The dose of alpha agonists is titrated slowly to avoid hypotension and if deemed ineffective, the medication should be tapered gradually over 1–2 weeks to avoid a sudden increase in blood pressure.[36] *Bupropion* (Wellbutrin, Zyban) is a third-line agent, which may be used off label if treatment failure occurs with stimulants, atomoxetine, guanfacine, and clonidine. Bupropion is a noradrenergic and dopaminergic reuptake inhibitor and has antidepressant properties. It is important to note that bupropion is associated with reducing the seizure threshold at high doses.[36]

Table 1:
Medications for the Treatment of ADHD and Their Side Effects

	Medications	Common Side Effects	Rare Side Effects
First-line agents	**Stimulants** Methylphenidates Amphetamines	Loss of appetite, nausea, insomnia, anxiety, headaches, palpitations, upper abdominal pain	Weight loss, growth retardation, chest pain, psychosis, seizures
Second-line agents	Atomoxetine Guanfacine Clonidine	Loss of appetite, nausea, constipation, abdominal pain, xerostomia, insomnia, fatigue, headaches, palpitation, erectile dysfunction, dysmenorrhea, urinary retention Fatigue, somnolence, headache, dry mouth,	Orthostatic hypotension, QT prolongation, seizures, agitation, mood swings, psychosis Constipation, decreased appetite, irritability
Third-line agents	Bupropion	Dizziness, headache, tachycardia, constipation, dry mouth, nausea, vomiting, anorexia, anxiety, insomnia	Seizures (dose related), sexual side effects, psychosis
Others	Tricyclic antidepressants	Blurred vision, dry mouth, constipation, weight gain, orthostatic hypotension	Seizures, cardiac arrhythmias, urinary retention, worsened narrow angle glaucoma

Non-Pharmacological Treatment of ADHD

Behavior Therapy:

Behavior therapy also plays an important role in ADHD, particularly with comorbid ODD.[49] It is based on social learning theory. In this form of therapy, the therapist identifies problem behaviors along with the preceding events and the reinforcers. A behavioral plan is put together to change the behavior by working on the triggers and avoiding the reinforcement of unwanted behavior. It involves parents and teachers along with the child.[50, 51]

Education:

Some modifications in the classroom environment can help children with ADHD significantly and improve their academic performance. Those with comorbid learning disorders may need an *individualized educational plan* (IEP) or even a special class or a resource teacher. It is also very important to educate the child, parents, and teacher about the symptoms, course, and treatment to provide the best possible treatment.

Child ADHD Case Vignette:

Kevin is an 8-year-old boy who presented to the child psychiatry clinic with his parents. He was referred to the psychiatrist by his school teachers. Kevin is the first born of 3 siblings and was born via *normal vaginal delivery* (NVD) without any antenatal complications. His mother consumed alcohol weekly during pregnancy and smoked up to one pack of cigarettes per day. His birth weight was 2.4 kg/5.3 lbs, with a normal *Appearance, Pulse, Grimace, Activity, and Respiration* (APGAR) score. He was breast-fed for a year and weaning started at 6 months of age. He achieved developmental milestones

on time. His mother reports that he has always been a very "active" child. She describes him as if "driven by a motor." It was very difficult for him to sit in one place, which caused them a lot of embarrassment in social settings. He would frequently get punished for his behavior.

He started school at 4 years of age, and the first year went smoothly. Since then, he has been having trouble in school. His teacher reports that he disrupts the class very frequently, roams around during group and individual activity time, and talks excessively in class. During playtime, he gets into fights with classmates, as he will not wait his turn. The same thing happens at lunchtime, as he tries to cut in line. His academic performance is declining now. He is competent in mathematics, but often makes careless mistakes while solving problems. He is struggling in science and English, especially with creative writing. The teachers provide him with extra time to finish his class work, but he is unable to do so despite the extra time. He takes a lot of time to finish his written assignments and makes a number of errors. He routinely forgets his lunch bag in school, and the teacher now reminds him at the end of school, which is helping him.

On mental state examination, Kevin is a well-kempt boy of average height and lean build, cooperative, and engaged. He initially sat in a chair, tapping on the table in front of him and humming his favorite song, then got up and started exploring the room. He dropped his bag on the floor and kicked it to one side while moving around. He interrupted his parents and the examiner a couple of times to ask questions related to the environment. His speech was of normal rate, rhythm, and volume, his affect was euthymic, and his thought process was goal directed. He said he wanted to be a pilot when he grew up.

Based on the presentation of this case and the multi-modal management approach of ADHD, the treatment must include the following:

1. Psychoeducation of the parents about the symptoms, presentation, and course of ADHD.

2. An explanation of the role of medications in the treatment of ADHD and a discussion of the possible side effects with them.

3. A stimulant medication, starting with a small dose with the plan of titrating it after a few weeks to obtain the maximum benefits.

4. The dose may be reduced or the medication may be switched to another class if intolerable side effects occur.

5. A comprehensive treatment plan that would include psychosocial interventions, a plan for school, and structural changes at home that may help him.

Adult ADHD Case Vignette:

Mrs. Smith is a 31-year-old mother of two sons who has been working at a grocery store for the last 3 months. She has brought her 7-year-old son for a follow-up, as he was diagnosed with ADHD 2 weeks ago. Mrs. Smith reports that during her son's evaluation, she noticed that she has many of the same symptoms. She wants to know if adults could have ADHD.

On further inquiry, Mrs. Smith reports that she was an average student in middle school, but her grades deteriorated significantly in high school. She was not able to go to college due to her poor grades and started working in a food chain as a waitress. She lost her job within a month and has not been able to maintain a job for longer than a year. Her employers complained about her punctuality, her inability to pay attention to the directions given to her, and noted that she would forget important tasks and at times "zone out" during conversations. She would leave things for the last minute and would then feel overwhelmed and anxious. Mrs. Smith herself reports that she has always been a forgetful and distractible person. She needs a lot of time to complete small tasks, which leads to a lot of frustration. She procrastinates a lot and gets bored very easily.

She now feels frustrated and depressed on and off, as due to these "habits," she is not able to take care of her children. She is often late to pick them up and drop them off at school, and she has missed many of their important school events and appointments due to her forgetfulness. She tries to keep reminders and maintain "to-do lists," but these don't help her all the time. She does not report any substance abuse, any family history of psychiatric illness, or any medical comorbidity.

On examination, she is of average height and lean build, making appropriate eye contact. She looked restless in her chair and kept shaking her leg during interview. She was attentive during the initial part of psychoeducation, but later did not seem to be concentrating on the information provided. At the end of the interview, she forgot her car keys on the desk and came back a while later to get them.

1. How would one diagnose ADHD in Mrs. Smith, who is 31 years old, based on the DSM-5 criteria?

2. Should we consider a stimulant, non-stimulant, or something off label?

3. Should the treatment algorithm be different in adults?

Conclusion

ADHD is a neurodevelopmental disorder affecting around 5% of children and adolescents worldwide. The core symptoms include inattention, hyperactivity, and impulsivity, based on which subtypes can be diagnosed. The symptoms need to be present before the age of 12 years for at least 6 months and must cause significant impairment in functioning. The disorder has a strong biological etiology, but environmental factors also play an important role. The biological treatment includes stimulants and amphetamine derivatives as first-line agents. This is followed by clonidine, guanfacine, and atomoxetine as second-line agents. Bupropion is the third-line agent used in the treatment of patients who are either intolerant to other agents or are not responsive. Behavior therapy and IEPs play an important role in the management of many individuals with ADHD. ◗◗

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Multiple-Choice Questions

53. **According to the DSM-V, symptoms of ADHD need to be present before what age for at least 6 months and must cause significant impairment in functioning?**

    A. 5 years

    B. 7 years

    C. 12 years

    D. 6 years

54. **The DSM-V ADHD criteria for inattention include all of the following, *except*:**

    A. feeling depressed

    B. reluctance toward tasks that require mental effort and disorganization

    C. difficulty sustaining attention and difficulty following through with instructions

    D. symptoms like distractibility, forgetfulness, losing daily necessities, or losing track of objects

55. **The most consistent structural brain imaging findings in children with ADHD include:**

    A. significantly smaller volumes in the dorsolateral prefrontal cortex

    B. significantly smaller volumes in the caudate and palladium

    C. significantly smaller volumes in the corpus callosum and cerebellum

    D. All of the above

56. **Which one of the following statements is correct about ADHD?**

    A. ADHD is a neurodevelopmental disorder.

    B. Core symptoms include inattention, hyperactivity, and impulsivity, based on which subtypes can be diagnosed.

    C. Behavior therapy and individualized education plans play an important role in the management of many individuals with the diagnosis of ADHD.

    D. All of the above

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Best Practices in CME

Attention-Deficit Hyperactivity Disorder:
Overview and DSM-5 Changes

Ayesha Mian MD, Sana Younus MBBS, and Asim A. Shah MD

ID#: L003377

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

This lesson addresses the gaps in knowledge of the new DSM-5 diagnostic criteria for ADHD, including an overview of the epidemiology, neurobiology, and several treatment modalities. This lesson also discusses two cases to illustrate diagnostic dilemmas.

Key Point 1: Functional Disability and Medical Care Costs

Patients with ADHD have higher medical care utilization and greater functional disability than the normal population. This lesson will make clinicians feel more equipped to deal with this often-challenging patient population and diagnose patients accordingly.

Key Point 2: Changes in the DSM-5

The most significant difference between the DSM-IV-TR and the DSM-5 is that the age criterion for the diagnosis of ADHD has changed from less than 7 to less than 12 years.

Key Point 3: A Multidisciplinary Approach is Needed to Treat ADHD

Effective treatment of ADHD requires a multidisciplinary approach with medications and behavior management.

Key Point 4: Adult ADHD Remains a Diagnostic Dilemma

Due to the lack of specific criteria for adult ADHD, it remains a diagnostic dilemma. One case vignette is included to allow for a better understanding.

Notes

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Dissociative Disorders: Between Neurosis and Psychosis

Cedric Devillé, Clotilde Moeglin, and Othman Sentissi

No commercial support was used in the development of this CME lesson.

KEY WORDS: Psychosis • Dissociative Disorders • Trauma

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) understand the various types of dissociative disorders, including recent changes made in the DSM-V; (2) convey the history and current diagnostic criteria for dissociative disorders; (3) understand the relationship between trauma and dissociative disorders; (4) explain the treatment options for dissociative disorders.

LESSON ABSTRACT: Dissociative disorders are a set of disorders defined by a disturbance affecting functions that are normally integrated with a prevalence of 2.4 percent in industrialized countries. These disorders are often poorly diagnosed or misdiagnosed because of sharing common clinical features with psychotic disorders, but requiring a very different trajectory of care. Repeated clinical situations in a crisis center in Geneva provided us with a critical overview of current evidence of knowledge in clinical and etiopathological field about dissociative disorders. Because of their multiple expressions and the overlap with psychotic disorders, we focused on the clinical aspects using three different situations to better understand their specificity and to extend our thinking to the relevance of terms "neurosis" and "psychosis." Finally, we hope that this work might help physicians and psychiatrists to become more aware of this complex set of disorders while making a diagnosis.

COMPETENCY AREAS: This lesson aims to address the gaps in learning in medical knowledge. Healthcare providers will gain knowledge in the area of dissociative disorders and distinguish them from other psychiatric disorders. In DSM-5, the dissociative disorders not part of, the trauma- and stressor-related disorders. Both acute stress disorder and post-traumatic stress disorder contain dissociative symptoms, such as amnesia, flashbacks, numbing, and depersonalization/derealization which can be difficult to distinguish from psychotic disorders because of their relationship to trauma and shared phenomenological elements. Readers will be more aware of these comorbid disorders and the presentation of symptoms as they make a diagnosis.

Introduction

Dissociative disorders are a complex syndrome because of multiple expressions and the wide variety, defined by disturbances of every area of psychological functioning, affecting functions that are normally integrated such as memory, consciousness, identity, emotion, perception, body representation, motor control, and behavior.[1]

Major changes in dissociative disorders in the recent fifth edition of DSM-5 include the following: (1) derealization is included in the name and symptom structure of what previously was called depersonalization disorder (depersonalization-derealization disorder); (2) dissociative fugue is now a specifier of dissociative amnesia rather than a separate diagnosis; and (3) the criteria for dissociative identity disorder were changed to indicate that symptoms of disruption of identity may be reported as well as observed and that gaps in the recall of events may occur for everyday and not just traumatic events. Also, experiences of pathological possession in some cultures are included in the description of identity disruption.

According to ICD-10, there are more subtypes of diagnostic categories and depersonalization/derealization disorder is classified in neurotic disorders (see Table 1).

Table 1:
Classification of Dissociative Disorders in ICD-10 and DSM-5

ICD-10		DSM-5	
F44.0	Dissociative amnesia	300.12	Dissociative amnesia without fugue
F44.1	Dissociative fugue	300.13	Dissociative amnesia with dissociative fugue
F44.2	Dissociative stupor		
F44.3	States of obsession and dissociative trance		
F44.4	Dissociative motor disorders		
F44.5	Attacks of cramps dissociative		
F44.6	Sensitivity disorders and dissociative sensory		
F44.7	Mixed dissociative disorders		
F44.8	Other dissociative disorders		
F44.80	Ganser's syndrome		
F44.81	Multiple personality	300.14	Dissociative identity disorder
F44.89	Other specified dissociative disorders	300.15	Other specified dissociative disorders
F44.9	Unspecified dissociative disorders	300.15	Unspecified dissociative disorders
F48.1	Depersonalization/derealization disorder (up to neurotic disorders)	300.6	Depersonalization disorder (up to dissociation disorders)

These classifications admit that dissociative disorders are psychogenic, that is, of purely mental origin.[2] At the present time, experts on this field agree that classifications and definitions of this disorder are insufficient.[3]

The prevalence of dissociative disorders is close to 2.4 percent in industrialized countries[4] and, for dissociative identity disorder, the prevalence is close to 1 percent.[1] The authors believe that these results are often undervalued.[5] The sex ratio is 1 : 1.[6]

Diagnostic of dissociative disorders can overlap with psychotic disorders, reflecting the close relationship between these diagnostic classes.[7, 11] This may contribute to diagnostic errors and therefore lead to inadequate care and treatment management.

The history of the concept of dissociation goes back to the works of Charcot and Bernheim on hysteria and hypnosis and then those of Janet and Freud. With Bleuler, the concept of "dissociation" extends and is soon permanently reduced to some symptoms of schizophrenia, known from clinicians as "Spaltung," a psychic disintegration expressed in discordant manifestations of thoughts, affects, and behavior. This division contributes,

even at the present time, to supply issues on the border, sometimes blurred, between hysterical symptoms, post-traumatic stress, and schizophrenia.

"The dissociation would focus on the body representation, in the direction of a separation of body and psyche (…)".[12] Dissociative disorders correspond to a less archaic way than schizophrenia, with an important sensory oppression component recognized by the evoking apprehended foreign sensations.[12] Laferrière-Simard and Lecomte[10] mention authors, including Janet (1894), Follin, Chazaud and Pilon (1961) who suggest the terms of madness and hysterical psychosis. Freud sometimes describes psychosis as an aggravated neurosis and Henry Ey thinks of neurosis as "a first degree of fall in psychosis."[12] In 1993, van der Hart et al.[13] suggest the term of dissociative reactive psychosis, instead of hysterical psychosis, diagnosed when an immersion in phenomena of traumatic origin becomes invasive for the patients. The psychotic characteristics would decrease or disappear when the traumatic origins are identified. In 2004, Ross and Keyes[14] suggest the existence of a distinct group of people who suffer from schizophrenia, with dissociation as the underlying expression of psychotic symptoms and, in this sense, they propose to create the subtype of dissociative schizophrenia like the paranoid or the catatonic subtypes.[10] We have therefore found, through the history of hysteria, that the terms psychosis and hysteria are contained in a single concept, to mention hysterical psychosis (in ICD-10, dissociative disorder conversion is also called "hysterical psychosis"). Since the 2000s, the new concept of dissociative schizophrenia emerges. So we have noticed that the term dissociative is once associated with neurosis and once with psychosis, or even both.

Moreover the dissociative disorders are frequently found in the aftermath of trauma, correlated or not with the emotional life during childhood.[15], [16] This latter consideration, shared by dissociative disorders and schizophrenia,[17] reinforces the communal phenomenological aspects and complicates the differentiation between these two clinical entities. Many of the symptoms, including embarrassment and confusion about the symptoms or desire to hide them, are influenced by the proximity to trauma. **In DSM-5, the dissociative disorders are placed next to, but are not part of, the trauma- and stressor-related disorders,**

also reflecting the close relationship between these diagnostic categories. Both acute stress disorder and post-traumatic stress disorder contain dissociative symptoms, such as amnesia, flashbacks, numbing, and depersonalization/derealization.

We have evaluated and managed several clinical cases of dissociative disorders in the crisis center of area-catchment of Jonction in Geneva, each one with distinct causes. To refine the diagnosis and optimize the care management of these clinical cases, we have performed a critical overview of current computerized evidence of knowledge (Medline).

Clinical Vignettes

Clinical Vignette Number 1:

Mr. A is a 32-year-old patient of Swiss origin. He works as an insurer. He has a partner whom he has been with for over 2 years and with whom he had a child. He talks about sexual abuse from one member of his own family members in the past but has only vague memories of this event. A diagnosis of paranoid schizophrenia was established 6 years ago, and the patient has been in remission for 5 years without antipsychotic treatment. The patient has contacted us to request a diagnostic evaluation in the context of a development.

With regard to mental status, the patient is calm and collaborating; his thoughts have an organized structure; he is well-oriented, and his hygiene and clothing are appropriate. His thymia is neutral and there are no elements of depressive symptomatology. His speech is coherent, fluid, and informative without delusional elements. His only "psychosis-like" symptomatology is the "voice hearings" in the form of voices that speak to him from within. He determines that these voices are coming from his own imagination.

Indeed, he describes constant oscillations between the presence of two distinct personalities, which he manages to differentiate. The first personality is described as that of a junkie (if he does not control himself, he lives as a person who needs to consume

drugs and he goes into hiding in uninhabited buildings), and the other personality is described as that of a conformist modern man (i.e., clean looking, "well thinking," and conforming to society's standards; an attitude he adopts elsewhere, at work, for example).

His mental status reveals the characteristics of a dissociative identity disorder. There are two distinct identities or "States of personality" in this patient; they take turns at controlling the behavior of the patient. The disturbance is not due to the direct effects of a substance or a general medical condition. Moreover, he does not have psychotic symptomatology. He describes that the voices are coming from the inside of himself (each of the personalities interacts with him, alternately). He has no other comorbid disorder. He has one meeting a month for supportive psychotherapy. He is not treated with psychotropic medication.

Clinical Vignette Number 2:

Mrs. B is a 44-year-old patient who has been married for 24 years; she lives with her husband and their 2 teenage children. She has no known psychiatric history. The authority of parenting has been a traumatic experience, and she has a self-assertion deficit.

She consulted the psychiatric emergency department in 2012, accompanied by her family. She presented with a behavior disorder of gradual emergence, in the form of psychomotor agitation and "sexual" exhibition. She also had voice hearings (she hears from "an angel" coming from inside that predicts upcoming events and guides her). The self-criticism is retained. The emergency psychiatrist felt that this was a psychotic disorder not otherwise specified; he administered an anxiolytic medication (lorazepam) to quickly tranquilize the patient and transferred her to the crisis center. Upon admission, the patient had significantly intense anxiety, had a situational mild to moderate spatiotemporal disturbance, and was confused. Her mood was sad, with mi-

nor anhedonia and minor abulia. She had a sleep disorder for three days, with insomnia at the beginning and at the end of the night. Her speech was coherent, informative, fluid, and critical in the aftermath (she says that she hears the voice of an angel, which she identifies as a production of her own imagination). Considering the persistent "psychosis-like" and mass anxiety symptomatology, antipsychotic treatment with olanzapine was administered, and it was recommended that the patient stays a few nights in the center for further care. The presence of a comorbid depressive disorder (MADRS scale score of 19) led us to prescribe an antidepressant treatment, trazodone; the dose was increased gradually to 200 mg per day. The "psychosis-like" symptomatology started improving quickly, within 48 h, and the antipsychotic treatment was stopped. The patient was able to return home after 3 days and was followed up every week with two interview sessions. During her follow up, thymic improvement was noted, with a return of the vital impetus and a decrease in the anxiety but with the emergence of a diffuse painful syndrome. Her treatment is one-session psychotherapy per week and trazodone 200 mg per day.

Clinical Vignette Number 3:

Mrs. C is a 33-year-old patient who is a law graduate. She is married and does not have any children. She presented with a major depressive disorder of moderate intensity, generalized anxiety, and a history of alcohol dependence (having been sober for a few months). She was hospitalized for the first time in the psychiatric department for 10 days, a few weeks before we met her, due to a diagnosis of "acute and transitory psychotic disorder" (with voice hearings and a behavioral disorder that has medicolegal impacts), which has been linked to disulfiram treatment; the evolution of this disorder has been favorable with olanzapine 10 mg/day and then quetiapine 200 mg/day, in addition to the usual treatment of venlafaxine 75 mg/day. Subsequently, this patient was treated in our ambulatory unit, where

risperidone 1 mg/day was prescribed, and then she was hospitalized again in the psychiatric clinic for one month. Venlafaxine was replaced by escitalopram. The dose of escitalopram was decreased to 30 mg/day as a result of an increase in her liver enzymes. We also substituted pregabalin for olanzapine 5 mg/day (which was reintroduced during the 2nd hospitalization), because of increased feelings of depersonalization-derealization, which means a feeling of "getting out of her body," which she described "as if" she was an automaton and having recurring feelings of being detached from herself. The patient had an improvement in her depressive symptomatology (MADRS score of 32 at admission and 12 over the course of treatment) under escitalopram 30 mg/day and pregabalin 200 mg/day. However, there was a persistence of moderate anxiety. She did not have any psychotic symptomatology. She benefitted from analytical psychotherapy with one meeting per week.

Discussion

The growing clinical interest in the different forms of dissociative disorders has led us to carry out a brief review of the literature, supported by three clinical cases to highlight this complex disorder. **Dissociative disorders are difficult to distinguish from psychotic disorders not only because of the close proximity of phenomenological elements but also because of a linked aetiology due to trauma, triggering sometimes both disorders. This is further complicated by other comorbid disorders, which are often present. Authors have reported association with an anxiety disorder,[18]-[21] a depressive state,[19]-[20] a borderline personality disorder, PTSD, or substance abuse (in 83 to 96% of cases of dissociative identity disorders)[1] and comorbid somatoform disorders (headache, in 79 to 91% of cases of dissociative identity disorders, conversion syndromes, and somatoform disorders in 35 to 61% of cases of dissociative identity disorders).[1]**

We noted that Mrs. B presented conversion symptoms (formerly classified as hysterical), which were theatrical (there was powerful staging in front of her family) with sexual thematic (showing off nude in front of her close

relations and people in her immediate environment), and she had voice hearings (pseudohallucinations).[22, 23] The latter were described as arising from the inside (and not from the outside); in fact the morbid conscience was retained; she criticized these voices by explaining they were produced by her imagination. This patient reported becoming an outside observer of her own body with a sense of being in a dream while maintaining an intact appreciation of reality, after following treatment and with a refinement of diagnostic criteria. These symptoms and their clinical and therapeutic progression (she had good anxiolysis with lorazepam) helped us to diagnose a specified dissociative disorder. The developed diagnostic could have led us to make an incorrect diagnosis of a brief psychotic disorder if we had not investigated for the presence of dissociative disorder. The diagnosis of dissociative disorder had a real impact on the patient's treatment.

However, there are only limited data on the effectiveness of drug treatments for dissociative disorders. The psychopharmacological approach is the foremost treatment based on the presence of other comorbidities. *Selective serotonin reuptake inhibitors* (SSRIs) treatment allows for the reduction of comorbidities, such as anxiety and depressive symptoms, although SSRIs have little effect on the dissociative disorder itself. We treated the patient with an antidepressant to reduce both the depressive and anxiety symptomatology and the pains associated with the symptoms. Psychotherapeutic support was given in the form of psychodynamic and systemic inspiration.

The symptoms Mr. A presented were likely to generate a diagnostic error, being the differential diagnosis between a psychotic disorder and a dissociative disorder close in this case. We established a diagnosis of dissociative identity disorder for this patient, who was previously diagnosed with schizophrenia. In fact, 25 to 50% of people diagnosed with a dissociative disorder are already affected by schizophrenia.[24] Voice hearings, for example, are found in 73% of schizophrenia cases[25] and in 82 to 87% of dissociative identity disorder cases.[26] In a 2005 paper, Kluft[27] describes that, for people suffering from a dissociative identity disorder, 80% of cases perceive their voice hearings as coming from inside of themselves (pseudohallucinations), whereas, for people suffering from psychosis, 80% of cases perceive their voice

hearings as coming from an external source (auditory hallucinations). Mr. A's medical files stated that he never had a disruption of behavior nor significant delirium for a period longer than one month. This is important because these patients tend to spend more time in the health care system. In fact, they have a diagnosis and treatments which are often poorly adapted.[28] This patient did not accept a psychoactive treatment. In this case, a supportive effective therapy with attentive listening was the adequate treatment without comorbidity.

Concerning the treatment of Mrs. C, she had received a diagnosis of acute and transitional psychotic disorder treated with an antipsychotic treatment. However, this was called into question due to the traced history of the post-crisis symptomatology. She described feeling detached from herself, of "getting out of her own body," she described voices heard internally (pseudohallucinations), and she retained morbid conscience, in the context of mass anxiety. These elements enabled us to diagnose a depersonalization-derealization disorder, which is a dissociative disorder according to DSM-5 but which is considered as a neurotic trouble in ICD-10. Concerning patients with depersonalization-derealization, they frequently use the expression "it is as if"[29, 30] to describe the state of their symptomatology. She presented comorbid disorders: a major depressive disorder associated with a generalized anxiety.

This patient received treatment with pregabalin for generalized anxiety and a selective serotonin reuptake inhibitor (escitalopram) for major depressive disorder but received no other treatment for the depersonalization-derealization disorder. Antipsychotic drugs are sometimes used to treat the depersonalization-derealization disorder; however, their effectiveness has not been demonstrated in any controlled study, and the emergence of depersonalization-derealization has been reported under antipsychotics.[31, 32] It is possible that the antipsychotic treatment she received previously could have enhanced this syndrome subsequently. The psychotherapy established for this patient was based on both the psychodynamic and systemic approaches.

The therapeutic approaches used for dissociative disorders correspond to the three basic models: cognitive-behavioral, psychodynamic, and systemic therapy. Psychotherapeutic treatments, which appear to be the most effective so far, are the EMDR,[33] the psychodynamic approach,[33], [34] and attentive listening to the words of the patient.[34] A few systemic approaches (of narrative inspiration, e.g.) provide interesting perspectives.[35]

We assume that it is important to distinguish voice hearings experiences coming from inside (pseudohallucinations) in the dissociative disorder from those coming from outside (auditory hallucinations) in psychosis.

We have identified that dissociative disorders are a kind of trouble close to psychotic disorders because of voice hearings experiences inter alia. The "psychosis-like" symptoms (behavioral disorders, agitation, (auditory) pseudohallucinations, and pseudodelusions) are a part of dissociative disorder, giving this diagnosis hard to make. Other "psychosis-like" symptoms are the confusion and the impression to be in a "dream," to be detached from feelings and to live something "as if." We are aware that this is specific of depersonalization-derealization disorder, a dissociative disorder according to the DSM-5.

Finally, the specific symptoms we described in this paper allowed us suggesting that dissociative disorders are a set of troubles at the border between neurosis and psychosis. The main question of this work was to know if the dissociative disorders belong to the group of neurosis or to the one of psychosis. Are they on the border between these two entities as the clinical symptomatology and the history show us? The fact that this disorder frequently appears among patients, especially with a borderline personality disorder, points the argumentation of this discussed border leading to prospects for theoretical model of dissociative personality structure.[36] If we agree that dissociative disorder shares the same concept of hysteria which is a neurosis, that ICD-10 mentions the term "hysterical psychosis," and also that depersonalization-derealization disorder is considered as a neurotic disorder even when we identify that it presents "psychosis-like" symptoms, this means that there is neurosis in psychosis and vice versa and thus that dissociative disorders are a separate entity. Concerning perspectives theories, it would be interesting to develop the idea that neurosis and psychosis are precarious terms, as the boundary between both is becoming increasingly blurred.

Conclusion

Adequate and well-adapted therapeutic treatment for these clinical cases of dissociative disorders has resulted in a favorable outcome in our crisis center. We have identified that dissociative disorders are a kind of trouble close to psychotic disorders on one hand, because of voice hearing experiences inter alia, and close to neurotic disorders on the other hand, because of intact reality testing inter alia. We therefore suggest keeping focus on descriptive clinical symptomatology in this case. Further clinical studies, theoretical approaches, and reflections about this complex disorder are suitable.

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Hatherleigh's Note: Additional typeface treatment was added to text for emphasis. Supplementary title page information, CME, Best Practices, and medication trade names were also included. British English spellings were changed to US English.

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Multiple-Choice Questions

57. **Dissociative Disorders most frequently occur in the aftermath of:**

    A. trauma, whether based in childhood or adulthood.

    B. eating disorders.

    C. traumatic brain injuries.

    D. childhood sexual abuse.

58. **Why is it difficult to distinguish dissociative disorders from somatiform disorders?**

    A. Dissociative patients often lie about their condition, causing misdiagnosis.

    B. The brain scans required to distinguish between the disorders are often not covered by insurance.

    C. Both disorders share phenomenological elements and have a linked aetiology.

    D. Patients with somatiform disorders only develop distinguishing symptoms after six months of treatment.

59. **What is the psychopharmalogical approach to treating dissociative disorders?**

    A. Drug treatment is never recommended for dissociative disorders.

    B. Psychiatrists are advised to immediately begin treatment with antipsychotic medication.

    C. Medication is only prescribed for patients with a history of traumatic brain injury.

    D. Psychopharamalogical treatment of comorbid disorders is recommended in conjunction with treatment of dissociative disorders.

60. **What is the prevalence of dissociative disorders in industrialized nations?**

    A. 10%

    B. 18.6%

    C. 2.4%

    D. .0067%

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Best Practices in CME

Dissociative Disorders:
Between Neurosis and Psychosis

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This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Dissociative disorders are a complex syndrome because of the wide variety of disturbances to psychological functioning. Current research on dissociative disorders, indicates that they frequently develop in the aftermath of traumatic experiences in childhood or adulthood. These disorders can be difficult to distinguish from psychotic disorders because of their relationship to trauma and shared phenomenological elements; comorbidly occurring disorders also complicate the diagnostic process. There is little clinical evidence showing that psychopharmacological treatments are effective for dissociative disorders, but there is some evidence showing the effectiveness of psychotherapy.

Key Point 1: Complexity of Dissociative Disorders

Dissociative disorder effect every area of psychological functioning, upsetting an individual's memory, consciousness, emotion, perception, motor control, representation, behavior, and identity.

Key Point 2: Dissociative Disorders and Trauma

Dissociative disorders are frequently found in the aftermath of trauma, correlated or not with the emotional life during childhood.

Key Point 3: Dissociative Disorders in the DSM-V

In DSM-5, the dissociative disorders are placed next to, but are not part of, the trauma- and stressor-related disorders, also reflecting the close relationship between these diagnostic categories.

Key Point 4: Dissociative Disorders and Psychotic Disorders

Because of shared symptomatology and comorbid disorders, in addition to a shared relationship with trauma, it can be difficult to distinguish a dissociative disorders from psychotic disorders.

Notes

The "Three Buckets" Model
for Treating Posttraumatic Stress
Disorder (PTSD):
Medication, Therapy, and Everything Else

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KEY WORDS: Military • Veterans • Posttraumatic stress disorder (PTSD) • Complementary and alternative medicine (CAM) • Meditation • Animal-assisted therapy • Acupuncture • Transcranial magnetic stimulation (TMS)

LEARNING OBJECTIVES: Clinicians will be enabled to: (1) define PTSD and introduce a "three buckets" concept as an organizational framework for the variety of PTSD treatment options, (2) understand the appropriate use of selected CAM therapies and the limitations and advantages of these therapies, (3) consider the scientific basis for TMS as an emerging treatment for PTSD, and (4) identify additional resources to incorporate this technology into clinical practice.

LESSON ABSTRACT: PTSD is a complex psychiatric disorder with common comorbidities that can be difficult to treat. Conventional evidence-based therapies include trauma-focused cognitive behavioral therapy and certain antidepressants. However, these treatments may not be tolerated or preferred for many individuals for a variety of reasons, or they may only be partially effective. This lesson familiarizes the clinician with a variety of CAM treatment options for PTSD, as well as the rapidly growing use of TMS for PTSD. We review the basics of various meditation practices, animal-assisted therapy, acupuncture, and TMS and potential ways they can be incorporated into practice. The research on CAM will also be briefly discussed.

COMPETENCY AREAS: This lesson focuses on providing patient care. Healthcare providers will come away with a useful framework to approach their treatment of PTSD, with a specific focus on treatments that are not yet as evidence-based. This lesson helps providers to increase their knowledge of what these treatments are so they can have an informed and open dialogue with patients in planning their treatment.

Introduction

Posttraumatic stress disorder (PTSD) is a complex disorder that involves several cognitive, emotional, and behavioral responses to an experienced or witnessed trauma that persist longer than one month and cause dysfunction in the patient's life. An estimated 6.8% of Americans will suffer from PTSD in their lifetime.[1]

While PTSD continues to gain attention in the scientific literature and media, it is important to recognize that this is not just a disorder experienced by military service members. The patients who suffer from this disorder form a heterogeneous group and, not surprisingly, there is no silver-bullet treatment. Practitioners treating this disorder are best served by having an array of treatment options.

This review introduces the idea of the "three buckets" concept for PTSD treatment.[2] The first two buckets comprise the two broad categories of evidence-based therapies: medication and psychotherapy. The therapies in these two buckets have proven to be effective in large, randomized controlled trials. Our review focuses specifically on the "third bucket" that comprises "everything else." The "everything else" refers to treatments that have not yet been as rigorously tested but are nevertheless very helpful in certain individuals. This definition includes *complementary and alternative medicine* (CAM) and emerging treatments.

While there are many therapies within the third bucket that deserve attention, we highlight the ones that we have found most useful. These include meditation, animal-assisted therapy, acupuncture, and *transcranial magnetic stimulation* (TMS).

Current Definition of PTSD

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) is the 2013 update to the *American Psychiatric Association's* classification and diagnostic tool, which, in the United States, serves as a universal authority for psychiatric diagnosis.[3] This manual describes the criteria for the diagnosis of PTSD.

DSM-5 criteria now identify the trigger to PTSD as exposure to actual or threatened death, serious injury, or sexual violation. The diagnosis of PTSD is currently based on 8 criteria from the DSM-5.

The first 4 criteria pertain to the "actual event" and must result from one or more of the following scenarios, in which the individual:

1. directly experiences the traumatic event

2. witnesses the traumatic event in person

3. learns that the traumatic event occurred to a close family member or close friend

4. experiences first-hand repeated or extreme exposure to aversive details of the traumatic event

The disturbance, regardless of its trigger, causes clinically significant distress or impairment in the individual's social interactions, capacity to work, or other important areas of functioning. It is not the physiological result of another medical condition, medication, drugs, or alcohol.

Symptoms that accompany PTSD should be present for at least one month following the initial traumatic event and include the following: re-experiencing, avoidance, negative cognitions and mood, and arousal; more specifically:

- **Re-experiencing covers spontaneous memories of the traumatic event, recurrent dreams related to it, flashbacks, or other intense or prolonged psychological distress.**

- **Avoidance refers to distressing memories, thoughts, feelings, or external reminders of the event.**

- **Negative cognitions and mood represents myriad feelings, from a persistent and distorted sense of blame of self or others, to estrangement from others or markedly diminished interest in activities, to an inability to remember key aspects of the event.**

- **Finally, arousal is marked by aggressive, reckless, or self-destructive behavior, sleep disturbances, hypervigilance, or related problems.**

Common Comorbidities with PTSD

Trauma exposure can lead to a variety of negative mental and physical health sequelae beyond PTSD symptomatology, and as such, it is commonly associated with at least one comorbidity. In fact, according to National Comorbidity Survey data, 50% of patients with PTSD have three comorbid psychiatric diagnoses (16% and 17% have one and two additional psychiatric diagnoses, respectively).[4] Substance use disorders, depressive disorders, and anxiety disorders appear to be the most common comorbid psychiatric conditions; the prevalence rates of these disorders are two to four times higher in patients with PTSD than those without.[3]

Among physical conditions, perhaps the most striking evidence is for comorbid *traumatic brain injury* (TBI) and chronic pain. Regarding the former, among the subpopulation of American soldiers returning from Iraq and Afghanistan diagnosed with mild TBI, 62% screen positive for PTSD. This represents a nearly six-fold increase from the 11% of soldiers overall who screen positive for the disorder.[5]

For chronic pain, studies show up to one half to three-quarters of patients with PTSD have a significant chronic pain condition. Scioli-Salter et al. provide an interesting review that offers insight into some of the shared underlying neurophysiology of the conditions and their implications for treatment. Importantly, they note that patients who have both conditions experience more pain, emotional distress, and disability than patients with either condition alone.[6]

With this information in mind, it is key to consider a patient's comorbidities when prescribing treatment. For example, knowing that a patient suffers from chronic pain may lead a provider to consider acupuncture over other CAM modalities, as acupuncture is often commonly used to treat pain as well.

The "Three Buckets" Concept

We have already briefly introduced the concept of our three bucket framework. **To review, the first bucket is evidence-based medication options; the second bucket is evidence-based psychotherapy options; the third bucket is "everything else"—i.e., options that have** not yet been evidenced in multiple large, randomized, controlled trials.

While many of the therapies in the third bucket are starting to accumulate more rigorous empirical support, most are still in the anecdotal phases of evidence accumulation. Some, such as meditation and acupuncture, have their roots established in thousands of years of tradition but little scientific theory. These have their origins in ancient Asian medicine traditions. Others in this bucket, such as TMS, are rooted in Western medicine and scientific theory but are just emerging as tested therapies for PTSD.

We encourage an open dialogue between patients and practitioners to help choose a regimen that works for them. Before delving deeper into the pros and cons of the third bucket, it is helpful to briefly review the first two and why patients may shy away from them.

Medications can be very helpful for PTSD. The first line is usually the antidepressant classes of *selective serotonin reuptake inhibitors* (SSRIs) or *serotonin and norepinephrine reuptake inhibitors* (SNRIs). Side effects are usually mild, such as dizziness and nausea. These usually go away in a few days.

More problematic side effects are sexual ones, which include delayed erections and decreased libido. These effects can usually be managed, for example, by switching medications, taking drug holidays, or by adding phosphodiesterase inhibitors, such as *sildenafil* (Viagra). However, it is important to ask about these or risk nonadherence and the patient not returning for a follow-up appointment.

Additional medication options include the alpha-blocker *prazosin* (Minipress), which is not yet FDA-approved for PTSD-related nightmares but is frequently used for this purpose. The main limiting factor for this medication is orthostasis. Patients should thus be educated to get up slowly from lying down.

Many practitioners prescribe second-generation antipsychotics (usually *quetiapine* (Seroquel) or *risperidone* (Risperdal) for refractory or partial response cases. The evidence for the use of these agents is not as strong as for the aforementioned medications, and they carry significant health risks in their association with metabolic syndrome (i.e., weight gain, diabetes, and hyperlipidemia).[7] However, clinical evidence points to their utility in some cases.

The second bucket includes all trauma-focused cognitive-behavioral therapies, such as exposure therapy (including virtual reality exposure therapy)[8] and *cognitive behavioral therapy* (CBT). In general, this process includes talking about the trauma and reducing the anxiety associated with it. There are two main limiting factors specific to this approach. First, patients may not be able to tolerate the increased anxiety they experience during sessions. Second, they may have an inability to establish a good therapeutic alliance.[9]

Understanding these limitations and the reasons our patients drop out of treatment can help us address this problem. Unfortunately, a recent study shows that only 52% of soldiers who screened positive for PTSD received minimally adequate care (four or more visits in six months), and 24% dropped out of care.[9] Of those who dropped out, 39% reported not liking the medication offered and two-thirds reported some form of discomfort with the mental health professional, e.g., that the practitioner was not adequately caring, communicative, or competent.

Therefore, understanding these limitations of the first two buckets (or approaches), we endeavor to discuss how treatments from the third bucket can be incorporated into practice.

Complementary and Alternative Medicine

First, it is important to clarify terms. According to the National Center for Complementary and Integrative Health (NCCIH) at the *National Institutes of Health* (NIH), "complementary" refers to non-mainstream practices that are used **together with** conventional medicine, and "alternative" medicine is the term used when a practice is used **in place of** conventional medicine.[10] These practices are increasingly integrated into conventional medicine (prompting the use of another related term, "integrative medicine").

CAM is commonly used by military members with PTSD (45% of active duty military versus 38% of civilians use CAM).[11] The *Veterans Affairs* (VA) healthcare system reports that nearly 90% of their facilities offer CAM (mostly meditation), according to a 2011 survey.[12] This survey was reported during a meeting held in 2011, sponsored by the VA's Office of Research and Development. The meeting included experts from the VA, Department of Defense, and National Institutes of Health on CAM for PTSD and concluded in deciding to fund several ongoing clinical trials on meditation.[13] They also conducted a review that identified seven randomized controlled trials and two nonrandomized studies of CAM for PTSD.[14] They found the strongest evidence (moderate) of the benefit of acupuncture and recommended more rigorous study on this method and meditation.

Our review will focus on three areas of CAM for PTSD in which we have the most experience and for which the most evidence is available: meditation, canine therapy, and acupuncture. Many other CAM techniques are used for PTSD. A more in-depth look at these other techniques is available in the book *Posttraumatic Stress Disorder and Related Diseases in Combat Veterans.*[15]

Meditation

Meditation is the most widely used CAM for PTSD.[12] It is a self-management approach that is safe, cost-friendly, portable, and easy-to-learn. The "self-management" aspect of meditation is often considered one of its greatest strengths in that it empowers patients to take an active role in their own healing process and gives them a sense of control over their symptoms.

Meditation can be broadly conceptualized as a form of "mental training." It has a long history rooted in ancient cultures and has evolved to take numerous styles. Most research on meditation for PTSD focuses on three broad types: *mindfulness meditation* (MM), mantra meditation, and compassion meditation.[16]

MM has been the most well-studied type of meditation and has additional evidence that it may be useful in patients with comorbid conditions such as depression, substance use disorders, sleep disturbances, and chronic pain.[16] Thus, it may be preferred in patients with these comorbidities. However, the best choice for the patient will largely depend on which practice most resonates with him or her (and to which they most likely will adhere), availability, and the teacher's experience.

Regardless of the type of meditation, there is evidence of the activation of a common cognitive pathway wherein the benefits of meditation for PTSD may be derived. A recent quantitative meta-analysis of 10 functional neuroimaging studies across many different meditative practices showed the activation of the

left caudate body, the left entorhinal cortex, and the medial prefrontal cortex during medidation.[17] While the significance of these findings is still being determined, we know that many of the symptoms of PTSD, such as hyperarousal and persistent fear states, correlate with an overactivation of the amygdala and that activation of the prefrontal cortex can help regulate this response, leading to greater stress tolerance and self-acceptance.[18, 19]

Mindfulness Meditation:

MM has a primary focus on breathing with the aim of achieving open, nonjudgmental awareness and acceptance. Research findings consistently demonstrate that this form of meditation produces improved health-related quality of life and well-being as well as reduced avoidance, depression, and numbing symptoms. Furthermore, there is some evidence that it has beneficial effects on other conditions such as hypertension and substance use disorders.[20]

Mantra Meditation:

Mantra meditations are a group of meditations that include mantra repetition, transcendental meditation (TM), and relaxation response training that use the common technique of repeating a word, phrase, or sound. This process aims to redirect the person's attention from rumination and maladaptive thought patterns, instead creating a sense of peace and relaxation.[21, 22] Similar to MM, mantra meditations have been shown to reduce the symptoms of PTSD.[23, 24] This reduction in symptoms is thought to be mediated through a physiologic relaxation response.[23, 25]

Mantra repetition, specifically, has been associated with an increase in existential spiritual well-being that may contribute to its overall health and mental health benefits. Researchers cite the importance of the spiritual meaning of the words selected by the individual and their potential power in eliciting feelings of well-being and self-confidence.[24, 26]

Compassion Meditation:

Compassion meditation emphasizes a sense of "lovingkindness" to all beings. It takes many forms, but it is primarily informed by Buddhist practice. Tonglen is one specific type of compassion meditation that is based on the Tibetan Buddhist tradition and involves the visualization of transforming another person's suffering into compassion.[27]

Several studies suggest that compassion meditation has several positive outcomes that would benefit patients with PTSD. Like other meditative forms, compassion meditation has been shown to reduce hyperarousal. It additionally increases social connectedness, which can translate into improved social support and personal relationships, which are key to recovery. Finally, compassion meditation has been shown generally to both increase positive emotions and reduce negative effects, which may, among other obvious benefits, improve the patient's capacity for resilience, making a case not just for its use in recovery but also in the prevention of PTSD.[15, 26, 28–32]

Animal-Assisted Activities and Therapy

Two of the main categories of incorporating animals into health care are animal-assisted activities, most commonly in the form of service dogs, and animal-assisted therapy.

Animal-Assisted Activities:

The *Americans with Disabilities Act* (ADA) defines "service animals" as animals that have been individually trained to do work or perform tasks to aid a person with a disability.[33] The ADA specifically identifies calming a person with PTSD as one such specific task, but it is important to distinguish these kinds of highly trained dogs from pets whose sole function is to provide emotional support. The service dog designation allows for the dog to accompany the person with PTSD in all areas of facilities where the public is normally allowed to go. Service dogs of veterans may be qualified to receive veterinary care benefits through the VA, and we recommend checking with your local branch.

Animal-Assisted Therapy:

Scientific evidence demonstrating improvements in symptoms of PTSD as a result of canine and equine therapy lags behind the remarkable growing interest and popularity of these programs. However, a growing body of evidence shows that the nurturing involved in this type of therapy provides positive sensory stimulation that can activate the anti-stress and pro-social neural and neurohormonal networks (e.g., increase oxytocin) in both humans and animals.[34–38] Furthermore, interactions with animals have been shown to lower blood pressure and have a calming effect on individuals with dissociative disorder.[39, 40]

The mere presence of animals in a healthcare setting may even be therapeutic. Studies have shown that their presence can increase individuals' willingness to enter into therapy, facilitate the therapeutic alliance, reduce the rate of attrition, and reduce symptoms of trauma.[41–43] **One recent study found that adults who wrote about a recalled trauma in the presence of dogs found the exercise less distressing and had significantly fewer symptoms of depression at follow-up than those who completed the writing exercise without a dog.[33]**

Animal-assisted activities and therapy can be challenging to incorporate into practice; we recommend looking thoroughly into local resources, ensuring the program is reputable and will fit your patient's needs. When done correctly, this type of therapy appears to be particularly beneficial to patients who struggle with more of the avoidance and isolation symptoms of PTSD; the animals can help serve as a bridge to broader, healthier social interactions.

Figure 1:
Photograph from National Intrepid Center of Excellence (NICoE) Facebook page.

Photo available online: https://www.facebook.com/NationalIntrepidCenterofExcellence/photos/a.10150163476202035.299199.156392117034/10153289164492035/?type=3&theater

Acupuncture

Acupuncture is an ancient treatment that utilizes thin, filament-like needles placed on the body to treat a variety of health (and even spiritual) problems. Its foundation is in *traditional Chinese medicine* (TCM), but since its first use thousands of years ago, it has been adopted by cultures all over the world, leading to a multitude of different practice styles and philosophies. However, the core aspects of the treatment remain the same.

Acupuncture was originally developed around a concept of a circulating life force known as *qi*. This concept has elicited a great deal of skepticism and controversy and is not adopted as a framework by all practitioners. However, it is useful to note at least for historical reference.

Qi is thought to be conducted between the surface of the body and internal organs via 12 main and 8 secondary pathways called meridians. The concept suggests that the normal flow of qi can be disrupted by the opposing forces of yin and yang, influenced by environmental factors such as illness, trauma, and stress. Acupuncture targets points along the meridians in an effort to balance yin and yang and restore the normal flow of qi.[46]

Modern scientists, who may or may not subscribe to the above theory, have attempted to explain some of the perceived benefits of acupuncture through other means. However, the clinical application of modern research on acupuncture is often limited by the study design, sample size, the selection of appropriate controls, and the non-standardized selection of points based on traditional methods of diagnosis and treatment.[47]

While the specifics of this nascent research go beyond the scope of this review, some of the research is starting to point to possible mechanisms such as the release of endogenous opioids; the modulation of neurotransmitters, such as serotonin, norepinephrine, dopamine, and GABA; effects on neurotrophins and cytokines to reduce inflammation; effects on the autonomic nervous system; and the regulation of the neuroendocrine system.[48–50] Each of these factors is known to be dysregulated to some degree in patients with PTSD.

In regards to how acupuncture fares against conventional treatments for PTSD (or waitlist controls), the evidence is again mixed but seems generally favorable. A systematic review of four *randomized controlled trials* (RCTs) and two uncontrolled trials were reviewed and had several important findings. One high-quality RCT showed significant improvements (i.e., on a self-report posttramatic symptom scale and three other outcome measures) compared to waitlist controls, but not significantly greater than the improvements seen with CBT. Two lesser-quality studies, one of which had a high risk of bias, showed that acupuncture plus

moxibustion (another TCM technique) was superior to oral SSRI therapy for PTSD.[51]

As with all CAM, we emphasize the need for more large, RCTs before acupuncture can be considered as a first-line treatment. The extant literature is encouraging, however, and acupuncture remains an excellent choice for adjunctive therapy for PTSD, particularly in patients with comorbid chronic pain.

Transcranial Magnetic Stimulation (TMS)

TMS is a noninvasive brain stimulation technique that is FDA-approved for the treatment of depression in patients who do not respond to at least one antidepressant in their current episode. Given its efficacy in the treatment of depression and its promise as a more benign, localized brain stimulation therapy alternative to ECT, it continues to be vigorously researched and used off-label for a variety of additional uses.

Without going into technicalities that are beyond the scope of this review, TMS devices use a coil placed near the patient's scalp to generate an electromagnetic current. This current stimulates a change in flow of the ionic current of the electrically conductive neuronal tissue, leading to neurotransmitter release. This local stimulation in turn can have downstream effects on additional neural networks, leading to broader effects—these effects will vary depending on the region targeted.[52]

Rossi et al have successfully used TMS as a diagnostic technique to measure brain GABAergic and glutamatergic tone. Using a paired pulse technique, they reported in 2009 that 20 drug-naïve patients with PTSD had reduced GABAergic tone in the bilateral hemispheres and increased glutamatergic tone in the right hemisphere.[53] Animal models have also demonstrated reduced GABA levels in the setting of chronic unpredictable mild stress and that TMS reversed these neurochemical changes.[54] These findings together suggest the stimulation of the left *dorsolateral prefrontal cortex* (DLPFC) and inhibition of the right DLPFC as a potential pulse sequence model for PTSD.[55,56]

Currently, two manufacturers license TMS machines for use for major depression: MagVenture (the MagVita system) and Neuronetics (the Neurostar system). They offer training for practitioners considering incorporating this therapy into their practice. Treatment for depression typically involves treatment 5 times a week for 4–6

weeks; research is ongoing to determine whether similar durations are necessary for PTSD and other conditions.

Figure 2:
Targeting the Brain Area for TMS

Lt. Col Geoffrey Grammer with a medical student volunteer, demonstrating how to pinpoint the target brain area for TMS. Photo taken on March 29, 2009 at Walter Reed Army Medical Center by Kristin Ellis. Available online: https://www.flickr.com/photos/36255477@N06/3374935325.

Others

The foregoing is not an exhaustive list of CAM or emerging therapies for PTSD. Additional treatment modalities include:

- **Yoga**

- **Exercise therapy**

- **Art therapy**

- **Emerging psychotherapies such as** *Accelerated Resolution Therapy* **(ART)[57]**

- *Cranial electrotherapy stimulation* **([CES] e.g., alpha-stimulation technology)[58]**

- **Stellate ganglion block[59]**

These therapies are wide-ranging; some of them require robust training by the practitioner (e.g., ART), some can be costly (e.g., CES), and others are low to no cost and are generally recommended by physicians to treat and prevent any health conditions (e.g., exercise). **Thus, we almost always recommend exercise to all patients, unless there is some physical contraindication,**

particularly given its demonstrated beneficial effects in many psychological conditions, including PTSD.[60–62]

Conclusion

PTSD is a complex disease that can be difficult to treat. There are numerous barriers to adequate care, including limitations to the more established, evidence-based treatments. Providing additional options as adjuncts or alternatives can increase the likelihood of successful treatment. We encourage providers to work with patients to determine what is effective for them. We cannot yet predict which treatment modality works best for any one individual, although individual patient factors, such as comorbidities and predominant symptoms, can help guide treatment choices. The discussion among patients and providers should include what treatments are most accessible and affordable for the patient, and providers should be familiar with local resources that offer these services. ◗◗

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Multiple-Choice Questions

61. **Which of the following criteria are necessary to diagnose PTSD?**

    A. Hallucinations

    B. Hyperarousal

    C. Disorganized behavior

    D. Somatic symptoms

62. **The "three buckets" concept for PTSD refers to:**

    A. a broad framework for the major categories of treatment modalities.

    B. three broad patient archetypes based on symptom clusters.

    C. complementary, alternative, and emerging treatments (CAM) for PTSD.

    D. three main pharmacotherapies for PTSD (SSRIs, prazosin, atypical antipsychotics).

63. **Which brain region, which is also a target region for TMS, does meditation appear to activate?**

    A. Hippocampus

    B. Frontal cortex

    C. Amygdala

    D. Prefrontal cortex

64. **According to the lesson, which of the following is generally recommended to every patient?**

    A. Fish oils

    B. Meditation

    C. More exercise

    D. Prazosin

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Best Practices in CME

The "Three Buckets" Model
for Treating Posttraumatic Stress Disorder (PTSD):
Medication, Therapy, and Everything Else

By COL (ret) Elspeth Cameron Ritchie, MD, MPH; and L.T. Kyle J. Gray, MD, MA

ID#: L003379

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

PTSD is a complex psychiatric disorder with common comorbidities that can be difficult to treat. Conventional evidence-based therapies include trauma-focused cognitive behavioral therapy and certain antidepressants. However, these treatments may not be tolerated or preferred for many individuals for a variety of reasons, or they may only be partially effective. This lesson familiarizes the clinician with a variety of CAM treatment options for PTSD as well as the rapidly growing use of TMS for PTSD. The authors review the basics of various meditation practices, animal-assisted therapy, acupuncture, and TMS and potential ways they can be incorporated into practice. The research on CAM is also be briefly discussed.

Key Point 1: "Three Buckets Model"

There are three main categories of treatment modalities for PTSD treatment, which we term the "three buckets model."

Key Point 2: Complementary, Alternative, and Emerging Treatments (CAM)

By definition, **CAM** and other emerging treatments lack the quality of evidence as the first two buckets of evidence-based therapies but have unique advantages; we recommend discussing each of the three buckets with patients.

Key Point 3: Neurobiology in PTSD

Evidence from meditation studies and **TMS** studies implicate the importance of the prefrontal cortex in mediating an overactive amygdala in patients with **PTSD.**

Key Point 4: Role of Exercise in PTSD

Regular exercise may also alleviate symptoms of PTSD, and because of its overall beneficial health effects, we recommend it to all patients.

Notes

Chronic Pain, Cognitive Deficits, and Depression

Karen M. von Deneen, DVM, PhD; Jixin Liu, PhD;
Jie Tian, PhD; and Yi Zhang, PhD

No commercial support was used in the development of this CME lesson.

KEY WORDS: Chronic pain • Cognitive deficits • Depression

LEARNING OBJECTIVES: This lesson will enable clinicians to (1) define chronic pain and understand its causes, (2) identify various cognitive deficits associated with chronic pain, (3) discuss possible treatment and proactive interventions for chronic pain and cognitive defects, and (4) depict how depression is diagnosed and treated in chronic pain patients.

LESSON ABSTRACT: Individuals suffering from chronic pain can have impaired higher-level cognitive skills, including executive function impairment and depression. Most clinics do not properly assess the extent to which these conditions affect patients' daily lives. Many neuroimaging studies have shown that alterations in the gray and white brain matter cause cognitive dysfunction, which presents itself in chronic pain. Therefore, it is critical to devise individualized treatment for chronic pain sufferers after a battery of neuropsychological tests.

COMPETENCY AREAS: This lesson addresses the gap in knowledge in the areas of patient care and practice-based learning and how to improve the treatment of patients with chronic pain and related complications, such as cognitive deficits and depression. Upon the conclusion of reading this lesson, readers will have a better understanding of chronic pain conditions and how to assess and manage issues associated with cognitive deficits/depression.

Introduction

Chronic pain (CP) is a condition lasting longer than 6 months and is defined as "a state of continuous learning, which has a close connection with an unconditionally pain-related stimulus, without the opportunity to disrupt the association with continuous pain" (Apkarian et al).[1] It includes *fibromyalgia* (FMS), *osteoarthritis* (OA), *migraine*,[2] chronic lower-back pain, *whiplash-associated disorders* (WAD),[3] etc. As depicted in Figures 1 and 2, this results in functional alterations in the brain that affect various neural circuits, such as working memory, response inhibition, mental planning, mental flexibility, and emotion/behavior monitoring.[4, 5] As brain function continuously reorganizes during chronic pain, new learning may be associated with the altered pattern of functional connections between brain regions.[2] CP causes physical and emotional stress in both patients and their loved ones, including increased healthcare costs.[6]

Figure 1:
Negative Effects of Chronic Pain on Emotion and Cognition
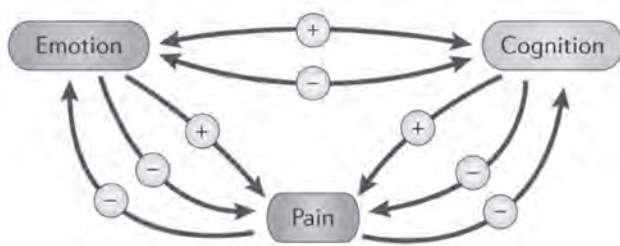
Pain can have a negative effect on the emotions and cognitive function. Conversely, a negative emotional state can lead to increased pain, whereas a positive emotional state can reduce pain. Similarly, cognitive states such as attention and memory can either increase or decrease pain. Of course, emotions and cognition can also reciprocally interact. The minus sign refers to a negative effect and the plus sign refers to a positive effect (used with permission).[4]

Prevalence, Etiology, and History of Chronic Pain, Cognitive Deficits, and Depression

Understanding the prevalence, etiology, history, and mechanisms of CP and its sequelae is crucial for diagnostic purposes and treatment in routine clinical practice and clinical trials. The prevalence of CP ranges from 7-40%, mainly being seen in women ages 45-65.[7] Approximately

50% of CP sufferers complain of cognitive deficits[8] and perform poorly on cognitive function tests.[9] One study provided a comprehensive overview of cognitive deficits found in CP cases. There are two theories to explain what causes CP. The first is known as the limited resources theory, which states that the brain's processing of pain stimuli disrupts other cognitive processes.[10] The second theory is called maladaptive plasticity, which holds that nociceptive signals lead to alterations in the central nervous system's structure and neurochemistry,[11, 12] leading to an overly active *amygdala* (AMY) and a deactivated *prefrontal cortex* (PFC).[13] An intact AMY-PFC pathway is crucial to cognitive and decision-making activities.[14] Some interesting findings related to CP have been that neurocognitive defects are correlated with age; CP may cause the early onset of aging, and CP results in decreased neurocognition as age increases[15, 16]. Overall, the exact mechanism behind CP and the related cognitive defects is not completely understood nor is how the secondary effects of CP, including depression, anxiety, and insomnia, evolve. It is known that depression and anxiety negatively affect cognition.[17] Approximately 40-50% of CP patients suffer from depression, and 20% of those score abnormally on neurocognitive tests.[18] CP and psychiatric disorders share neural pathways[19] and directly affect one another;[20] hence, together they pose a greater danger than they do by themselves.[21] Certain studies suggest that altered moods result in cognitive impairments in many CP cases.[22, 23] In 2009, one group of researchers found decreased gray matter density in patients suffering from CP and depression; thus, neurocognitive defects were attributed to both.[24]

Assessment and Diagnosis of Chronic Pain, Cognitive Deficits, and Depression

Neuropsychological assessments and executive function evaluations are not routinely assessed in pain management clinics because there is no easily administered gold-standard battery of tests for CP. Most importantly, executive function deficits can be difficult to assess using only paper tests and cannot fully evaluate daily life situations.[17, 25] Some assessment tools used in CP are best described by Ojeda et al (2015).[26] One such comprehensive test, called BRIEF-A, can

assess multiple executive function defects seen in various conditions,[27, 28] including CP.[29] Other specific types of neurocognition and tests that measure them are as follows: **attention and information-processing speed** (the *Symbol Digit Modalities Test and Trail-Making Test*); **working memory** *(the Paced Auditory Serial Addition Test* or *Spatial Span*); **memory** (the *Rey Auditory Verbal Learning Test* and *Rey Complex Figure Test)*; and **executive functions** (the *Wisconsin Card Sorting Test* for **mental flexibility**, the *Stroop test* for **cognitive inhibition**, and the *Controlled Oral Word Association Test* for **verbal fluency)** [see ref. 30 for details regarding each test].

Figure 2:
Psychological Processes and Behavioral Consequences Involved In Chronic Pain
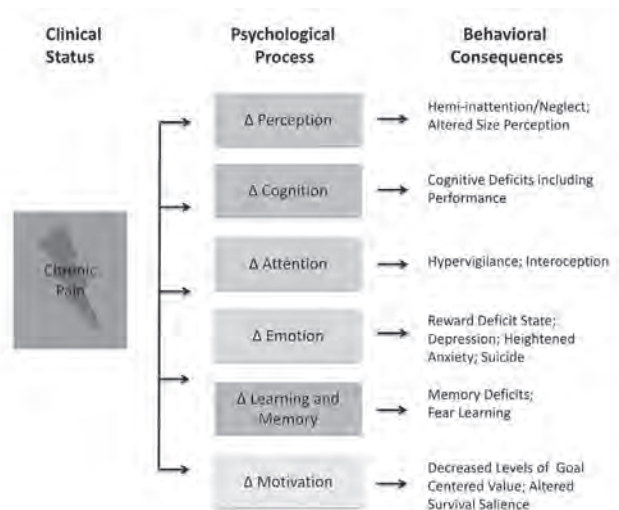
Following pain (a sensory or emotional experience to an actual trauma or perceived bodily threat), a number of psychological processes, including those listed here, are involved in the response. These change processes may be resilient or resistant to the inciting events or become altered, as noted in examples of behavioral consequences. Additionally, alterations in one system may have consequences for another. The understanding of how these systems interact and can be targeted will have significant implications for treatment approaches (used with permission).[5]

Treatments and Treatment Issues

Following the diagnosis and assessment of CP, the next step is educating the patient, on an individual basis, about how to manage and cope with his or her condition, cognitive deficits, and depression.[31, 32] Then, he or she can be given coping strategies with which to reduce functional disability, such as internal memorization techniques[33] and external memory cues.[34] Some specific examples include the following: for *processing speed*, Time Pressure Management is a strategy-based system for living with reduced processing speed that was originally developed for patients with concussions or brain injuries;[35] for *attention* difficulties leading to inattentiveness and forgetfulness, the patient may be encouraged to set alarms or smartphone notifications as reminders of particular tasks; *working memory* strategies include mental or out-loud rehearsal of information;[36] and, for *executive function* difficulties, such as problems with planning and organization, creating a weekly planner and learning to follow a procedure that is broken down into logical parts are helpful.[37] For more strategy suggestions, see http://www.latrobe.edu.au/data/assets/pdf_file/0008/256922/focusing_attention.pdf. The predominant reason for implementing these strategies is that they aid in neuroplasticity.[38] Thus, a restorative approach includes repeated practice using standardized tasks that target specific cognitive domains.[39] One such method is *computerized cognitive training* (CCT), which includes game-like formats (CogMed, Lumosity, CogniFit, Posit Science, and SBTPro) intended to promote neural repair.[40, 41] Other recommendations include reading, card games, crosswords, or puzzles as well as learning new hobbies that are socially/physically interactive.[42]

Drug therapy can also be combined with the above-mentioned methods for better results in managing pain as well as cognitive deficits and depression. Agents such as anticholinesterases (for dementia), opioids (these cause neuroplastic alterations and should be used with caution long-term),[43] benzodiazepines (chronic impairment of cognition),[44] tricyclic antidepressants (memory and psychomotor speed impairments),[45] selective serotonin uptake inhibitors (minimal effects on cognition),[46] anticonvulsants (treat neuropathic pain well),[47] and over-the-counter analgesics (mild effect on cognitive processes)[48] have been prescribed for CP and/or depression, but their side effects and further cognitive impairments must be discussed with each individual patient.[49] Alternative medicine or holistic approaches, including Traditional Chinese Medicine/acupuncture, have also been proven useful and lack many drug-related side effects.[50]

Cognitive-behavioral therapy (CBT) is a psychological therapy program for reducing depression and anxiety in CP patients.[51] This form of treatment involves relaxation and mindfulness techniques, managing stress, and muscle deconditioning to reduce pain.[52]

Physical exercise has been proven to not only alleviate pain and depression but to also enhance cognition.[53-54] The critical step is convincing the patient of the benefits of non-strenuous exercise, such as yoga,[55] tai chi, swimming, walking,[53] etc. These forms of exercise have neuroprotective effects[55] and decrease anxiety,[56] but more research must be done in pain populations.

Transcranial magnetic stimulation and direct current stimulation[57] via *electroencephalography* (EEG) and *functional magnetic resonance imaging* (fMRI) neurofeedback have also been shown to be effective methods of treating CP, cognitive deficits, and depression.[58] These stimulate the brain regions involved in the neural pain modulatory system[59] and cognitive networks to relieve CP,[60] improve working memory,[61] and regulate emotion.[62] Finally, to view all of the methods described in this section, please refer to Figure 3.

Figure 3:
Psychological Treatments and Functions for Chronic Pain Across Brain Systems
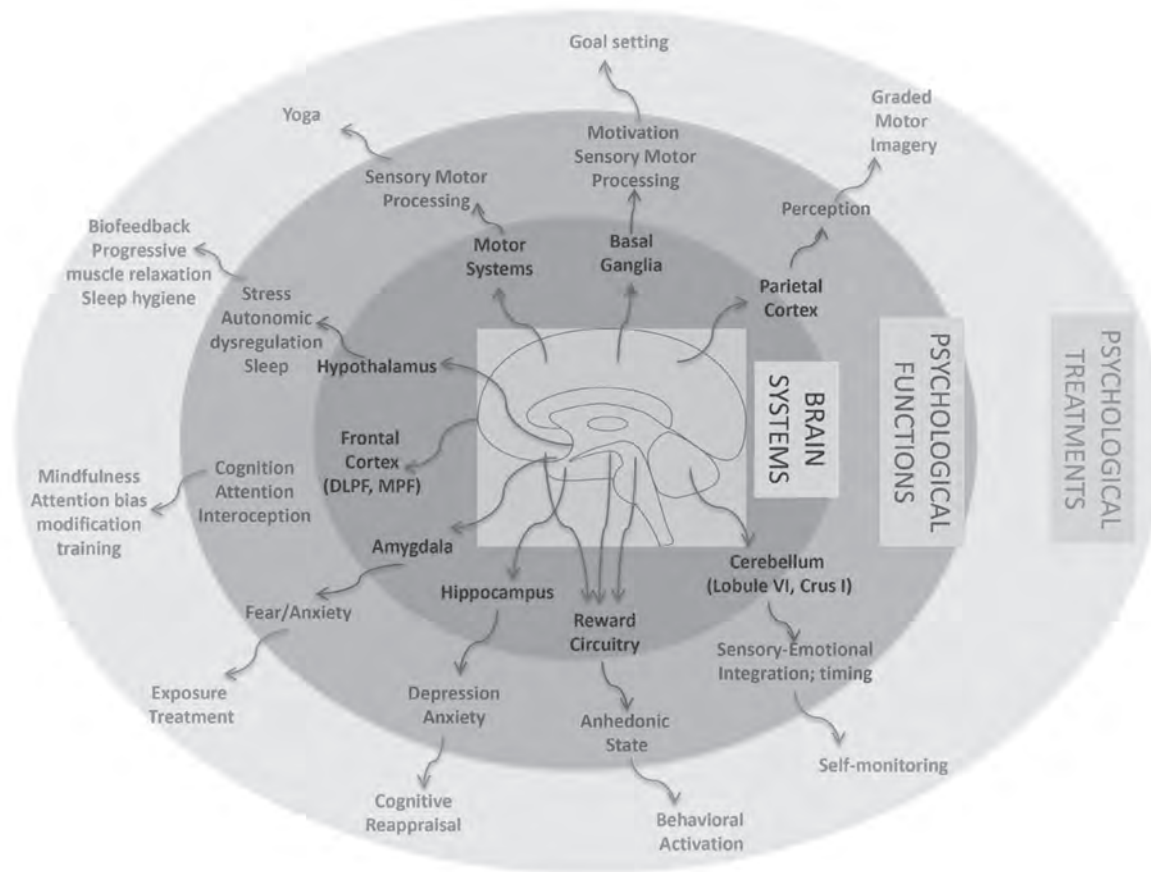
A network of brain systems underlies alterations in psychological function in the chronic pain state. This figure shows specific psychological treatments that target alterations in psychological function across brain systems (used with permission).[5]

Summary and Conclusions

Addressing the relationships between CP, cognitive deficits, and depression is a real issue in pain management clinics and deserves further study.[29] Thus far, no researcher has devised an experiment regarding the training of cognitive skills in CP with endogenous pain and mood control. Preventative interventions for CP and its effects must be systematically evaluated from the onset of injury, before they become chronic. The most important question remains whether clinical focus should be on decreasing the psychological aspects of CP first, directly targeting CP, or using a graded approach.[63] **Based on the research presented, it seems that the methods that produce the best results involve a combination of therapies and approaches in dealing with CP, cognitive deficits, and depression that is tailored to the patient's individual medical profile, needs, and goals.** 〽

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Multiple-Choice Questions

65. **What is the major cause of chronic pain?**

    A. Disregulated neural networks

    B. Elevated mood states

    C. Eating spicy food

    D. Living in a humid environment

66. **Which one of the following is *not* a cognitive deficit associated with chronic pain?**

    A. Decreased memory-related processes

    B. Increased pain

    C. Decreased motivation

    D. Anhedonia

67. **According to the lesson, what is the best method of treating chronic pain?**

    A. Physical exercise

    B. Cognitive-behavioral therapy

    C. A multifactorial approach/combination of therapies

    D. Drug treatment

68. **How do clinicians diagnose depression associated with chronic pain?**

    A. EEG

    B. CT

    C. MRI

    D. Neuropsychological assessment

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Best Practices in CME

Chronic Pain, Cognitive Deficits, and Depression

By Karen M. von Deneen, DVM, PhD; Jixin Liu, PhD; Jie Tian, PhD; and Yi Zhang, PhD

This valuable take-home reference translates the evidence-based, continuing medical education research, and theory acquired from reading the associated CME lesson into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to medical students, general practitioners, researchers, and family physicians, who may not have up-to-date knowledge about chronic pain and its medical consequences. Knowing the signs, symptoms, and sequelae of chronic pain can aid in prompt identification and treatment.

Key Point 1: Identification of Chronic Pain and its Consequences

The key to treating chronic pain is proactively identifying the symptoms at an early stage, before they progress to more severe pain, cognitive defects, and depression.

Key Point 2: Intervention

Immediate intervention that includes multifactorial approaches, such as cognitive behavioral therapy, pain/depression medications, and holistic approaches, prevents chronic pain conditions from progressing.

Key Point 3: Competent Staff

Seeking proper personnel and well-trained staff is important in the successful treatment of chronic pain and its sequelae.

Key Point 4: Continuing Education

Reading current research on chronic pain is important in preparing for its treatment and possible prevention. This includes working in interdisciplinary teams at university hospitals or research facilities dedicated to studying various types of strokes and providing current intervention methods.

Key Point 5: Research and Development

Being involved in chronic pain studies will help the scientific and medical community deal with chronic pain directly.

Notes

Biomarkers in Alzheimer's Disease

Carla Bejjani, MD; Raja Mehanna, MD; and Asim Shah, MD

No commercial support was used in the development of this CME lesson.

KEY WORDS: Alzheimer's disease • Biomarkers • PET scan • Aβ42 • Tau

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) understand the current hypothesis for *Alzheimer's disease* (AD) pathogenesis, called the amyloid cascade, (2) discuss the need for and the availability and clinical utility of biomarkers of AD, and (3) discuss different imaging strategies for AD and its findings.

LESSON ABSTRACT: AD is pathologically defined by the accumulation of extracellular aggregates of amyloid β sheets (Aβ) and intracellular neurofibrillary tangles, dystrophic neurites, and neuropil threads of tau protein. The current diagnosis of AD relies solely on clinical criteria. The failure of many phase III studies revealed a strong need for biomarkers of AD to improve the specificity of the diagnosis, thus ensuring that non-AD demented patients are excluded from AD trials, but also to allow an earlier diagnosis and attempt a disease-modifying treatment earlier in the pathological process to ensure a higher likelihood of success. In this lesson, we review the available imaging and biological markers of AD.

COMPETENCY AREAS: This lesson addresses the gap in knowledge and role of biomarkers in AD. The authors utilize informatics to improve the specificity of the diagnosis of Alzheimer's disease, which aids in early detection and treatment by the use of imaging and biological markers of AD.

Introduction

A progressive neurodegenerative disorder, *Alzheimer's disease* (AD) accounts for approximately 50%–60% of all cases of dementia.[1] Its incidence increases with age, and, with the increasing aging of populations and life expectancy, the prevalence of AD continues to rise worldwide.[2]

AD is pathologically defined by the accumulation of two types of proteins in the brain: (i) *amyloid β sheets* (Aβ), forming extracellular aggregates in the form of plaques and *cerebrovascular amyloid angiopathy* (CAA); and (ii) *tau protein*, which forms intracellular neurofibrillary tangles, dystrophic neurites, and neuropil threads.

Aβ is produced by two enzymes' sequential cleavage of *amyloid precursor protein* (APP). The prevailing current hypothesis for AD pathogenesis, called the amyloid cascade, suggests that Aβ aggregation is the initiating event in which the different stages of aggregates, from soluble oligomers to insoluble fibrils in plaques, impair synaptic function and ultimately damage neurons, resulting in chronic neurodegeneration, leading to cognitive impairment and finally dementia.[3]

An extensive number of large phase III clinical trials on Aβ targeting drugs have reported no beneficial effects on cognitive symptoms in patients with sporadic AD.[4, 5] One explanation is that the trials enrolled patients with AD and dementia, who are thus at too advanced of a stage of the disease to benefit from this type of drug. Clinical dementia is associated with severe neuronal and synaptic loss and a heavy tangle load that are not likely to benefit from arresting Aβ aggregation or plaque removal. This underlines the need for biomarkers allowing for the detection of subjects with AD pathology before clinical dementia (necessary for the clinical diagnosis) develops. In addition, AD clinical criteria are not specific enough, with AD trials ultimately enrolling only 80% of patients with genuine AD pathology,[6] creating yet another need for biomarkers to improve the specificity of the diagnosis.

The *National Institutes of Health* (NIH) defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[7] In 1998, the Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute of Aging Working Group stated that an ideal AD diagnostic biomarker should be able to detect a fundamental feature of Alzheimer's neuropathology, validated in neuropathologically confirmed AD cases, precise (able to detect AD early in its course and distinguish it from other dementias), reliable, simple to perform, non-invasive, and inexpensive.[6, 8]

Biomarkers for AD are, in fact, being developed and include the use of imaging techniques and measurements of the levels of proteins in the blood and the *cerebrospinal fluid* (CSF).

In this lesson, readers will review the current AD biomarker candidates, determine which ones are the most powerful, and understand the current research and clinical applications.

We will start by reviewing neuroimaging technologies as they provide a noninvasive or minimally invasive method for early AD detection.

Neuroimaging

AD is associated with progressive atrophy, synaptic dysfunction, as well as Aβ and Tau deposition. Structural *magnetic resonance imaging* (MRI) offers a volumetric measurements of the progressive atrophy from neuronal loss, information that can be valuable when assessing prognosis; synaptic dysfunction can be gauged with techniques measuring the fMRI *blood-oxygen-level-dependent* (BOLD) signal,[9] regional metabolism with *18F-2-deoxy-2-fluoro-D-glucose* (18F-FDG), and regional perfusion with 15O-water PET or single photon computed tomography (SPECT)[9,10] Aβ deposition in the brain is measured with several compounds, of which *(11)C-labelled Pittsburgh Compound-B* (11C-PIB) has been applied to the largest number of patients. Much less experience exists with specific tau markers, of which 18F-AV-1415 is the first reported, originally as 18F-T807.[11] 18F-FDG, amyloid, and tau studies are carried out using *positron emission tomography* (PET). Because metabolism and brain perfusion are coupled in AD, perfusion studies with SPECT provide information similar to 18F-FDG PET.[12] Although SPECT brain perfusion studies are easier to perform and less expensive than PET studies,[13] they have less spatial resolution, and thus less sensitivity and specificity, particularly at early stages of the disease.[14, 15]

We will now look at each of the aforementioned techniques in more detail.

MRI:

Structural MRI creates a three-dimensional image that evaluates the brain's physical structure. Serial MRIs performed in presymptomatic individuals have suggested that atrophy in some regions, particularly the precuneus and medial temporal areas, may start as early as four years of age, before the onset of cognitive impairment.[16] In cognitively normal elderly individuals, cortical thinning in precuneus and medial temporal regions has been found to correlate with subsequent cognitive decline as much as a decade later[17–19] or with amyloid deposition and reduced CSF Aβ.[20–22] The pattern of cortical thinning in people who will develop AD differs from that associated with the cognitive loss from healthy aging.[23] Regional atrophy correlates with regional Aβ deposition, particularly in the posterior cingulate cortex, in presymptomatic people or those with subjective cognitive complaints, but not in *Mild Cognitive Impairment* (MCI) or AD, suggesting that the damaging effect of Aβ occurs in the presymptomatic or very mildly symptomatic stages, when Aβ-reducing therapies should be applied.[22, 24, 25]

In patients with MCI, thinning of the temporal cortex and precuneus is a predictor of worsening AD, particularly when combined with neuropsychological, PET, and CSF markers.[26–29] Although atrophy can be appreciated visually,[30, 31] automated methods are more precise and facilitate longitudinal follow-up.[32–34] In one longitudinal clinical study, these methods had 67% sensitivity and 69% specificity to separate stable MCI from MCI worsening to AD, 86% and 82% to separate healthy controls from MCI worsening to AD, and 93% sensitivity and 85% specificity to separate healthy controls from AD.[26] In another longitudinal study with a 3-year follow-up,[28] the combination of greater learning impairment and increased medial temporal atrophy was associated with the highest risk: 85% of patients with both risk factors converted to AD within 3 years, vs 5% of those with neither.

Functional MRI:

Impaired synaptic function across the various AD stages can be gauged with techniques measuring the fMRI BOLD signal, regional metabolism, and regional perfusion. Findings are concordant, but each technique is amenable to different applications. Metabolism has been studied most extensively, but the most recent developments are the increasing use of resting state BOLD fMRI to assess functional connectivity changes and of *arterial spin labeling* (ASL) to measure regional perfusion using non-invasive MRI.[25]

18F-FDG PET Scan:

Regional cerebral metabolism studies with PET have used 18F-FDG as a metabolic marker.[35–37] The most typical pattern found in early AD is decreased metabolism bilaterally in the parieto-temporal association cortex and posterior cingulate gyrus.[27] Metabolism reflects synaptic activity and therefore is most affected early in the regions to which medial temporal neurons project,[38, 39] and may reflect impaired connectivity even in presymptomatic subjects.[40] As atrophy corresponds to neuronal loss, it is not surprising that the regions that appear most affected on volumetric MRI and metabolic PET do not coincide early in the disease,[41] but they partially overlap as the disease progresses.[42] As the disease progresses, some areas of the frontal association cortex become hypometabolic, while the paracentral cortex (primary motor-sensory areas) remains preserved. The specificity and sensitivity of these findings continue to be debated. In studies with neuro-pathological confirmation, the sensitivity (84%–95%) has been higher than the specificity (71%–74%); that is, a normal study is seldom associated with AD.[43, 37] **Among persons with MCI, those most likely to progress to AD have metabolic findings similar to AD. 18F-FDG PET may predict the worsening from MCI to AD better than structural MRI or SPECT.[15]**

Perfusion SPECT Scan:

The most commonly used tracers for studying cerebral perfusion with SPECT are Tc-99m *hexamethyl pro-pylamine oxime* (HMPAO, Ceretec™), a lipid soluble macrocyclic amine, and Tc-99m *ethyl cysteinate dimer* (ECD, Neurolite™). The pattern of decreased regional perfusion in the parieto-temporal cortex, hippocampus, anterior and posterior cingulum, and dorsomedial and anterior nucleus of the thalamus had a sensitivity of 86% and a specificity of 80% comparing AD to normal controls.[44, 45] In a group of 70 patients with dementia and 14 controls, all with autopsy, SPECT was most useful when the clinical diagnosis was of possible AD, with a probability of a diagnosis of AD of 67% without SPECT,

of 84% with a positive SPECT, and of 52% with a negative SPECT.[46] However, to predict the progression from MCI to AD, SPECT has been reported to have 41.9% sensitivity and 82.3% specificity,[47] although a meta-analysis assigned to SPECT a similar predictive value as MRI measurements.[15] A head-to-head comparison of perfusion SPECT with metabolism PET has shown that PET has much better sensitivity and specificity than SPECT in predicting AD.[35]

Aβ Imaging:

Brain Aβ has been imaged most extensively with "Pittsburgh Compound B" (11C-PIB),[48] helping separate the dementias with marked Aβ deposition from the rest. Patients with AD dementia have a 50%–70% increased retention (range 20%–80%) in global cortical 11C-PiB compared with cognitively normal older individuals.[49] PIB is only available bound to 11C, a positron-emitting isotope with a half-life of 20.4 minutes, but since 2012 Aβ-imaging compounds have been bound to 18F, with a half-life of 109.8 min. The longer half-life allows for the radiotracer to be synthesized at a facility with a cyclotron and then shipped to institutions with PET cameras, a process much less expensive than having an on-site cyclotron. These PET ligands include 18F-flutemetamol (Vizamyl), also called 3F-PiB or GE-067,[50] 18F-florbetapir (Amyvid), also called AV-45,[51] 18F-NAV4694, formerly known as AZD4694,[52] and 18F-florbetaben (Neuraseq), also called BAY94-9172 or AV-1.[53] Using these amyloid tracers, a 40%–70% increase in cortical ligand retention is found, but some show lower cortical binding in patients with AD than 11C-PiB, while others have higher nonspecific white matter binding than 11C-PiB.[52] **All these tracers are approved by the FDA for use in clinical settings.**

It is worth noting that PiB and the 18F PET amyloid ligands were developed to bind to aggregated Aβ with a preference for compact plaques and vascular deposits (CAA), while diffuse plaques are less prominently labeled and amorphous plaques comprising loosely aggregated Aβ containing little β–sheet structure do not bind PiB.[6, 54–56]

In early AD, 11C-PIB binds mainly to the fronto-parieto-temporal association cortex, sparing the paracentral regions and primary sensory cortex. It also binds to the striatum. The regional retention of PIB-like compounds reflects the regional density of Aβ plaques.[55–58] A positive amyloid PET scan is reported in 85%–90% of clinically diagnosed cases with AD dementia.[59] Approximately 90% of PiB-positive MCI cases progress to AD dementia during clinical follow-up, while most PiB-negative cases show stable cognition.[60–62]

Aβ brain deposition begins in the preclinical stages of AD, increases during the MCI stage, and, by the time of the AD diagnosis, remains relatively stable as the disease progresses.[63–65] Thus, it is a marker of the preclinical stages of the disease and correlates with the degree of cognitive impairment only in the preclinical stages and MCI, not during AD,[65–68] while atrophy and synaptic dysfunction continue to increase and spread as clinical AD worsens and cognition deteriorates.[25]

Aβ imaging is also a powerful tool to separate AD, characterized by Aβ deposition, from the fronto-temporal dementias, which develops without Aβ deposition. In that context, 11C-PIB and 18F-FDG have similar power.[25] On the other hand, Aβ PET has been reported negative in 14% of patients with AD symptomatology[69] or amnesic MCI patients.[70] This number may rise to 30% when the patients studied are older than 82 years.[71]

Hyperphosphorylated Tau Imaging:

In the healthy brain, the protein tau stabilizes neurotubules and is therefore essential for normal neural function.[72] However, in AD and other neurodegenerative disorders, tau becomes abnormally hyperphosphorylated, dysfunctional, and misfolded, constituting the tangles observed neuropathologically in AD and other tauopathies. The imaging compounds that we mention here do not bind to the healthy, native form of tau but to the abnormally folded tau, thus allowing only the pathological form to be visualized.[25] The first compound shown to bind to hyperphosphorylated tau is 18F-FDDNP,[73] which binds to Aβ as well, but with less imaging sensitivity and specificity than the PIB-like compounds.[74] It has shown increased binding in regions likely to have high tau, such as the medial temporal regions,[75, 76] which show relatively low 11C-PIB binding.[42] In the initial stages of use in humans are several tau-binding compounds that seem to have imaging characteristics superior to FDDNP. These compounds include 11C-PBB3,[77] 18F-T807, most recently known as 18F-AV-1451,[11, 78] and 18F-THK5117.[72] 11C-PBB3 is photosensitive and therefore difficult to use in practice; it also has a high level of uptake in the superior sagittal sinus. The most experience exists with

18F-AV-1451, which shows highly specific uptake in areas known neuropathologically to contain a large amount of tau in AD.[79] These ligands have not yet been FDA approved for diagnostic use in AD.

While their decreased invasiveness makes the neuroimaging technologies very desirable, CSF biomarkers remain the most established and studied biomarkers in the diagnosis or AD. We will discuss them in more detail in the section below.

CSF Biomarkers

The core pathological hallmarks of AD are the intracellular accumulation of abnormally hyperphosphorylated tau protein and the extracellular deposits of Aβ peptide. Because the CSF is in direct contact with the extracellular space of the brain and usually reflects pathological changes in the brain, it seems like an optimal source of biomarkers.[2, 80, 81]

Currently, the main biological biomarkers employed in AD diagnosis are total tau (t-tau), the isoforms of phosphorylated tau (p-tau181 and p-tau231), and b-amyloid peptide (Aβ42).[82–85]

Data from clinico-pathological studies show that CSF levels of total Tau reflect the intensity of neuronal degeneration, while p-tau reflects tangle pathology and Aβ42 is inversely correlated with Aβ plaque counts at post-mortem examination.[82–]

CSF Markers of Aβ Deposition:

Several proteins, peptides, and enzymes involved in the amyloidogenic APP processing can be measured in the CSF. These include different truncated species of Aβ, Aβ14 to Aβ16 and Aβ17 up to Aβ42,[86] *soluble b-secretase cleaved APP* (sAPPb),[87] and Aβ oligomers.[88, 89] Among these, only CSF Aβ42 is well established as a biomarker for AD.[6]

The measurement of Aβ in the CSF became an important candidate biomarker for AD after a report showing the secretion of Aβ in the CSF in 1992.[90] However, subsequent reports showed no clear change of CSF total Aβ in AD.[91, 92] Immunoassays specific for Aβ42 were developed after it was discovered that the 42 amino acid form of Aβ, Aβ42, was prone to aggregate and the earliest Aβ species deposited in plaques.[93, 94] Numerous studies since 1995 have shown a marked reduction in CSF Aβ42 in patients with AD dementia,[6, 95,] with a level approximately 50% of the age-matched cognitively normal individuals.[97] The absolute cut-off value varies with the measurement technique used, with values between 450–650 pg/mL for ELISA and 192 pg/mL for the Luminex xMAP technique.[6] However, the two techniques show a tight linear correlation.[98] In a recent meta-analysis, this test was found to have a pooled sensitivity of 80% and specificity of 76% in distinguishing AD from control or non-AD dementia.[99]

The lowering of CSF Aβ42 in AD is due to the peptide's aggregation in the brain, with an inverse correlation between low levels of Aβ42 and postmortem plaque load in cortical regions,[84, 100] and it precedes AD dementia onset by at least 10 years.[101–103]

In addition to helping with the diagnosis of AD, CSF Aβ42 might be useful in MCI patients as well as for treatment response evaluation. Indeed, multiple studies have shown that more than 90% of MCI patients progressing to AD dementia have low CSF levels of Aβ42 at baseline, while stable MCI cases have normal CSF Aβ42.[104–108] In addition, a transient lowering of CSF Aβ42 was reported in response to reduced Aβ production following BACE1 inhibitor treatment as well as in healthy volunteers.[109]

However, inter-individual variations in total Aβ production (of all Aβ isoforms) exists, and some AD cases that are "high producers" may have false negative Aβ42 tests; that is, the decrease in CSF Aβ42 is masked by the overall higher Aβ production. Conversely, some non-AD cases that are "low producers" may have false-positive Aβ42 tests, with a level just above the cut-off.[110, 111] Some authors suggest correcting this by the use of the CSF Aβ42:Aβ40 ratio, where Aβ40 is around 10 times more abundant than Aβ42 and not affected by AD. The reduction of Aβ42 (but not Aβ40) in AD leads to a reduction in this ratio that is more marked than the reduction in Aβ42 alone.[110, 111] Further validation is needed, as well as determining a cutoff AD diagnostic value for this ratio.

CSF Markers of Tau:

While quite sensitive for AD pathology, a reduction of CSF Aβ42 levels may also occur in other diseases, such as Lewy body dementia, vascular dementia, and cerebral amyloid angiopathy without AD.[113–115] Hence, although a decreased level of Aβ42 is suggestive of AD, it is not sufficient for a diagnosis of AD.

Total tau CSF levels are approximately 3 times higher in AD patients than in age-matched controls.[116] The specificity of this isolated biomarker is low, as total Tau protein levels can also be elevated in other acute neurodegenerative diseases and brain lesions, such as head trauma, stroke, and Creutzfeldt-Jakob disease.[80, 81, 113] On the contrary, p-tau protein (subtypes p-tau181 and p-tau231) is the most specific biomarker of AD, being normal in non-AD diseases, including those in which Tau protein levels may be increased.[113]

High levels of CSF total tau and p-tau seem also to be related to a faster progression of hippocampal atrophy[117–119] on MRI. These findings, however, need further validation.

Correlation Between the Different Biomarkers

Taken individually, each biomarker and imaging technique provides some information on one aspect of AD pathology. It is worthwhile to assess the correlation—and discordance—between them.

In the Aβ pathway, the lowering of CSF Aβ42 in AD is due to the aggregation of peptide in the brain, with an inverse correlation between low levels of Aβ42 and in vivo PiB binding in cortical regions.[6, 120]

Indeed, researchers have demonstrated an inverse correlation between global cortical amyloid PET ligand retention and CSF Aβ42 levels.[6] Overall, 88% of subjects in one study had concordant amyloid biomarker results, with either negative or positive amyloid PET scans and CSF Aβ42 levels.[6] A few had discordant amyloid biomarker results, with either normal CSF Aβ42 levels but positive amyloid PET scans (5.4%), or positive (low) CSF Aβ42 but normal amyloid PET (6.6%).[6] The existence of cases with discordance between CSF and PET amyloid biomarkers, particularly with low CSF Aβ42 but normal amyloid PET, has been a subject of discussion. Case reports initially suggested that early diffuse Aβ deposits, which bind amyloid ligands poorly, occur before fibrillar plaques, or that CSF Aβ42 reductions even before brain Aβ accumulation are sufficient to enable detection by PET.[121] **A larger study supported that this discordance (mainly isolated CSF Aβ positivity) was clearly related to an early disease stage.[122] Indeed, Aβ42 is**

more sensitive in the early stages of AD, while PET amyloid may still change dynamically during later stages of disease.[6] A recent study showed that the cortical flutemetamol retention levels correlate with disease stage in patients with MCI, while CSF Aβ42 levels do not.[123] However, large studies with longitudinal data sampling are needed to better understand the temporal relation between CSF Aβ42 and amyloid PET.

Aβ, MRI, and 18F-FDG abnormalities in healthy people with mean or median age in their 70s have been determined by two separate groups in the US using either PET (N=430) or CSF (N=311) to assess Aβ, yielding remarkably concordant results,[124–126] suggesting a prognostic value to these markers. At 1 or 5 years, the progression rate to MCI or dementia was 2%–5% for participants without abnormal Aβ or other preclinical markers, 11% for participants with only Aβ abnormality, 21%–26% for participants with Aβ plus MRI or 18F-FDG markers of AD, 43%–56% for participants having in addition subtle cognitive decline, and 5%–10% for suspected non-Alzheimer pathology or SNAP (MRI or 18F-FDG abnormalities characteristic of AD, but no Aβ deposition).[124, 127] Remarkably, in the Aβ PET study, the SNAP group did not differ from the groups with amyloid deposition in MRI and 18F-FDG characteristics,[127] leading to the conclusion that these changes may be independent of Aβ deposition in the brain. However, participants with abnormal Aβ had a greater rate of worsening to dementia and progressive worsening of MRI and 18 F-FDG parameters, not observed in the SNAP group, in a 15-month follow-up.[128] Over a 14-year follow-up, the progression to dementia of the SNAP group was only slightly higher than that of Aβ-negative, MRI-normal participants and lower than those with Aβ on PET and normal MRI.[126]

On the other hand, a large study comparing PET and CSF markers showed that amyloid PET was more strongly related to CSF tau and cognitive decline than CSF Aβ42, while CSF Aβ42 was more strongly related to possession of the apolipoprotein E (APOE) e4 allele than amyloid PET.[122] Other studies have shown that patients who are amyloid PET-positive have higher CSF t-tau and p-tau levels, but the correlations with CSF t-tau and p-tau are weaker than the strong inverse correlation found between amyloid ligand retention and CSF Aβ42.[6, 129–132]

A recent series analyzing the relationship between AD pathology in cortical brain biopsy and AD biomarkers in 182 AD patients[133] showed that the amount of amyloid plaques and hyperphosphorylated Tau in cortical brain biopsies were associated with low CSF Aβ42 and high CSF levels of tau markers, respectively. Another series reported a 94% concordance between CSF biomarkers and neuropathological diagnosis.[113] An AD biomarker profile (low Aβ42 associated with high levels of CSF total tau and p-tau) also distinguishes with high accuracy (up to 95% sensitivity) MCI patients who will progress to AD from MCI patients who will remain cognitively stable during the follow-up and from healthy controls.[105–108]

AD biomarkers might also have some prognostic value, as AD patients with extreme alterations in CSF biomarkers (Aβ42 reduction and increased total tau and p-tau) appear to progress unfavorably, with more severe cognitive decline, poor response to anticholinesterase treatment, and higher mortality.[134]

Finally, some authors advocate the use of the p-tau/Aβ42 ratio and report a sensitivity of 91.6% and a specificity of 85.7% for AD compared to neuropathology.[82] In one study, it was also the best biomarker for differentiating AD from the behavioral variant of frontotemporal lobar degeneration and from semantic dementia, with a sensitivity of 91.7% and 98.3%, respectively, and a specificity of 92.6% and 84.2%, respectively.[135]

Other Biomarker Candidates

In a recent meta-analysis of all CSF and blood biomarkers for the diagnosis of AD, Olsson et al[136] reviewed cohorts of patients with AD versus controls or patients with mild cognitive impairment due to AD versus those with stable mild cognitive impairment (i.e., not progressing to dementia at a follow-up of at least 2 years). They extracted data for markers of APP metabolism (Aβ42, Aβ40, Aβ38, and α and β cleaved soluble amyloid precursor protein [sAPPα and sAPPβ]), neurodegeneration (t-tau, *neurofilament light protein* [NFL], *neuron-specific enolase* [NSE], *visinin-like protein 1* [VLP-1], and *heart fatty acid binding protein* [HFABP]), tangle pathology (p-tau), glial activation (YKL-40, *monocyte chemotactic protein 1* [MCP-1], and *glial fibrillary acidic protein* [GFAP]) and blood–brain barrier function (CSF to serum albumin ratio) in the CSF and blood (serum or plasma).

The authors found that the core biomarkers differentiated AD from controls with good performance. CSF total tau and p-tau were on average 2.54 times (95% CI 2.44–2.64, p<0.0001), and 1.88 times (95% CI 1.79–1.97, p<0.0001) higher, respectively, than in controls, while the level of Aβ42 was almost 50% lower (0.56, 95% CI 0.55–0.58, p<0.0001) in AD patients than in controls. These markers also allowed differentiation between cohorts with mild cognitive impairment due to AD and those with stable mild cognitive impairment with average ratios of 0.67 for CSF Aβ42, 1.72 for p-tau, and 1.76 for t-tau.[136]

In addition, CSF NFL was helpful in differentiating between AD patients and controls (2.35, 95% CI 1.90–2.91, p<0.0001). The plasma levels of t-tau were also significantly higher in AD patients than in controls (1.95, 95%CI 1.12–3.38, p=0.02), but the variation in the few available studies was large; more data are needed to verify this association.[136]

CSF NSE, VLP-1, HFABP, and YKL-40 showed moderate differences between AD patients and controls (average ratios 1.28–1.47). Other assessed biomarkers had only marginal effect sizes or did not differentiate between control and patient samples.[6, 130]

The authors suggested that t-tau, p-tau, Aβ42, and NFL in the CSF should be used in clinical practice and clinical research.[136] However, there is no established cutoff for these tests. Indeed, there is significant variation in how different laboratories establish cutoffs for biomarker concentrations to differentiate patients with AD from controls. Furthermore, there is substantial variability in biomarker concentrations between laboratories and assays.[137]

A special note should be made that, in the meta-analysis from Olsson et al, the blood level of Aβ42 was not useful for distinguishing between AD and controls (average ratio 1.04, 95% CI 0.96–1.12, p=0.32) or between mild cognitive impairment due to AD and stable mild cognitive impairment (average ratio 0.81, 95% CI 0.53–1.24, p=0.32).[136] Similarly, plasma or serum concentrations of Aβ40 did not differ significantly between patients with AD and controls (average ratio 1.04, 95% CI 0.98–1.11, p=0.17 (136). No data were available for serum or plasma P-tau.

Clinical Practice

In autosomal-dominant AD, where the timing of the onset of dementia can be predicted with a certain level of accuracy, CSF Aβ1–42 declines 25 years before onset, followed by amyloid deposition, as measured by PET imaging 15 years before onset, along with increased CSF tau and hippocampal atrophy. This is followed by cerebral hypometabolism on 18F-FDG-PET about 10 years before onset.[25, 102] A similar sequence seems to be present with Aβ deposition in sporadic, late onset AD, although the etiologic mix in the more advanced age group yields more complex biomarker results.[138] P-tau deposition occurs in AD, but its timing in relation to Aβ deposition or to the onset of clinical symptoms has not been determined by in vivo studies.[25]

The amyloid biomarkers CSF Aβ42 and amyloid PET both show a high diagnostic ability to identify AD during the earlier stages of the disease. These biomarkers also demonstrate high concordance, with approximately 90% of cases being either positive or negative for both biomarkers. The high concordance for the amyloid biomarkers suggests that they may be used interchangeably to aid in clinical diagnostic work-up or patient enrichment in clinical trials.

Core CSF biomarkers for AD are a reduction in Aβ42, with an increase in t-tau and p-tau. The sensitivity and specificity of the combined use of CSF Aβ42, t-tau, and p-tau for the diagnosis of AD in the dementia or MCI stage reaches 85%–90%.[80] Values that are close to the cutoff should be interpreted with caution, as there is a continuum of values and an overlap between controls and patients with AD or MCI.[6] Furthermore, no clinically available cutoff has been determined for any of these levels, and each institution should establish an internally validated diagnostic cutoff value.

The choice between amyloid PET and CSF biomarkers as diagnostic tools in the clinic will depend on the availability, training status, and willingness among clinicians to perform lumbar puncture, the availability of and distance to PET scanners and cyclotrons, and finally, financial considerations that payers have to make (i.e., CSF analysis is more affordable than a PET scan).[6] Regarding side-effect profiles, post-lumbar puncture headaches, the main complication following a lumbar puncture, have an incidence of 1%–3%,[139–141] which is in the same range as the risk of headaches following amyloid PET.[6]

In 2007, the *International Working Group* (IWG-1) proposed research criteria for "prodromal Alzheimer's disease" requiring the presence of episodic memory impairment and at least one abnormal biomarker, either of molecular pathology (reduced CSF Aβ42, elevated CSF tau, or amyloid PET deposition) or topography (medial temporal lobe atrophy or FDG hypometabolism).[143]

Revised in 2014, the IWG-2 criteria allow for prodromal AD to be diagnosed in the presence of cognitive impairment in domains other than memory, or in the presence of either increased amyloid PET deposition or the combination of lowered CSF amyloid-β1-42 and elevated CSF tau.[144] In 2011, the *National Institute on Aging/Alzheimer's Association* (NIA-AA) reviewed diagnostic criteria for AD dementia.[145] **While recognizing the usefulness of biomarkers and calling laboratories to establish internally qualified cutoff values, biomarkers were not recommended for routine diagnostic purposes. However, these can increase confidence in a clinical diagnosis of AD and can be useful in certain circumstances, such as early-onset dementia and atypical presentations of AD in which the differential diagnosis includes other neurodegenerative diseases.**

In regard to MCI, the NIA-AA proposed new research/clinical criteria for MCI due to AD (MCI-AD).[146] These criteria allow for cognitive impairment in any domain (not only episodic memory) and incorporate combinations of amyloid (CSF or PET) or "neuronal injury" markers (medial temporal lobe atrophy, CSF tau, temporo-parietal FDG-PET hypometabolism). When combined, these markers allow several designations: (i) a high likelihood of MCI due to AD, i.e., MCI and both abnormal amyloid and neuronal markers; (ii) a low likelihood of MCI due to AD, i.e., MCI but normal/negative amyloid and neuronal markers; (iii) an intermediate likelihood of MCI due to AD where information from only one biomarker—either a neuronal injury marker or amyloid marker—is available, and that biomarker is abnormal, and; (iv) uninformative, i.e., MCI but biomarkers are unavailable, conflicting, or indeterminate. In cases in which amyloid markers are negative but measures of neuronal injury are positive, the term *MCI suspected non-Alzheimer's pathology* (MCI sNAP) has been proposed.[125]

It is uncertain how these criteria compare in their ability to detect MCI due to underlying AD and to predict the subsequent development of AD dementia, how easily each can be operationalized for use in multicenter cohort studies, and what can be concluded from cases with discordant biomarker results. Their use in clinical routine diagnosis of MCI cannot be recommended.

The accumulated data from clinical studies do not support the association of any specific biomarker of AD with the assumption of progression from normal cognition to AD in asymptomatic subjects; thus, the concept of "preclinical AD" is restricted only to research and cannot be translated into recommendations for clinical practice[2, 147] at this time.

Conclusion

The failure of many phase III studies has highlighted the strong need for biomarkers of AD to improve the specificity of the diagnosis, thus ensuring that non-AD demented patients are excluded from AD trials as well as to allow an earlier diagnosis and attempt a disease-modifying treatment earlier in the pathological process to improve the likelihood of success. In this lesson, we have reviewed the available imaging and biological markers of AD and their clinical applications. While these imaging findings and biomarkers are not yet part of the diagnostic criteria of AD, they can increase confidence in a clinical diagnosis of AD and can be useful in certain circumstances, such as early-onset dementia and atypical presentations of AD in which the differential diagnosis includes other neurodegenerative diseases. 》

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Multiple-Choice Questions

69. Which one of the following statements is true?

A. AD clinical diagnosis is specific enough for research and clinical purposes.

B. AD diagnostic criteria include the use of biomarkers.

C. Biomarkers increase the sensitivity and specificity of AD diagnosis, but they are not yet included in the diagnostic criteria.

D. None of the above.

70. Which one of the following statements regarding biomarkers of AD is correct?

A. CSF Aβ42 decreases only in AD and is thus very specific.

B. CSF total tau increases only in AD and is very specific.

C. The combination of reduced Aβ42 and increased total tau and p-tau in the CSF is the most sensitive and specific for AD.

D. The combination of reduced Aβ42 and increased total tau and p-tau in blood is the most sensitive and specific for AD.

71. Regarding the correlation between different biomarkers, all of the following statements are correct, *except:*

A. There is a 90% concordance between a CSF Aβ42 reduction and amyloid retention on PET scans in patients with AD.

B. AD core markers increase the risk of evolution from MCI to AD.

C. The risk of evolution from MCI to AD can be accurately predicted in any individual with AD core markers.

D. The CSF Aβ42 level changes 10 years before the amyloid PET scan.

72. Regarding imaging in AD:

A. Tau imaging by PET scan has been FDA approved for the diagnosis of AD.

B. Aβ imaging by PET scan has been FDA approved for the diagnosis of AD.

C. Brain MRI shows frontal and temporal atrophy.

D. Perfusion SPECT has much better sensitivity and specificity than metabolism for the diagnosis of AD.

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Best Practices in CME

Biomarkers in Alzheimer's Disease

By Carla Bejjani, MD; Raja Mehanna, MD; and Asim Shah, MD

ID#: L003381

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The current diagnosis of AD relies solely on clinical criteria. The failure of many phase III studies revealed a strong need for biomarkers of AD to improve the specificity of the diagnosis. In this lesson, we review the available imaging and biological markers of AD to help address the gap in knowledge about biomarkers in AD.

Key Point 1: Need for Biomarkers

There is a need for biomarkers of AD to allow better patient selection and earlier intervention in clinical trials.

Key Point 2: CSF Biomarkers

The core *cerebrospinal fluid (CSF)* biomarkers for AD are a reduction in Aβ42 and increases in T tau and P tau.

Key Point 3: Concordance between Imaging and CSF Biomarkers

Amyloid biomarkers CSF Aβ42 and amyloid PET have a high and early diagnostic ability, with high concordance between the 2 tests.

Key Point 4: The Use of Biomarkers

Biomarkers increase the sensitivity and specificity of AD diagnosis, but they are not yet included in the diagnostic criteria.

Key Point 5: Preclinical AD

A concept of "preclinical AD" is restricted only to research and cannot be translated into recommendations for clinical practice.

Notes

Substance Use During Pregnancy

Ariadna Forray, MD

KEYWORDS: Pregnancy • Substance use disorder • Breastfeeding • Tobacco

LEARNING OBJECTIVES: Clinicians will (1) review the different types of substance abuse that occurs in pregnant women; (2) understand the way in which substance use affects a developing pregnancy; (3) consider the common co-occurring conditions and disorders that impact pregnant women with substance use disorders, and; (4) understand the ways that breastfeeding may assist in relapse prevention.

LESSON ABSTRACT: Prenatal substance use is a critical public health concern that is linked with several harmful maternal and fetal consequences. The most frequently used substance in pregnancy is tobacco, followed by alcohol, cannabis and other illicit substances. Unfortunately, polysubstance use in pregnancy is common, as well as psychiatric comorbidity, environmental stressors, and limited and disrupted parental care, all of which can compound deleterious maternal and fetal outcomes. There are few existing treatments for prenatal substance use and these mainly comprise behavioral and psychosocial interventions. Contingency management has been shown to be the most efficacious of these. The purpose of this review is to examine the recent literature on the prenatal use of tobacco, alcohol, cannabis, stimulants, and opioids, including the effects of these on maternal and fetal health and the current therapeutic options.

COMPETENCY AREAS: This lesson serves to educate clinicians regarding substance use disorders in pregnancy. Clinicians will gain medical knowledge in identifying risks that pregnant patients with a substance use disorder may face. This lesson will review the evidence regarding treatment options and relapse prevention in pregnant women.

Introduction

In the United States, women comprise 40% of those with a lifetime drug use disorder and 26% of those who meet criteria for both an alcohol and drug use disorder during the prior 12 months.[1] Furthermore, women are at highest risk for developing a substance use disorder during their reproductive years (18–44), especially ages 18–29.[2] This means that women who are pregnant or soon to become pregnant are at increased risk for substance abuse. **According to a national survey conducted in the United States in 2012, 5.9% of pregnant women use illicit drugs, 8.5% drink alcohol and 15.9% smoke cigarettes,[3] resulting in over 380,000 offspring exposed to illicit substances, over 550,000 exposed to alcohol and over one million exposed to tobacco in utero. Similar patterns of use have been observed in Europe[4-5] and Australia.[6]** The most commonly used substance in pregnancy is nicotine, followed by alcohol, marijuana and cocaine.[7, 8] However, polysubstance use is as high as 50% in some studies.[7, 9] Recently, there has been an increase in opiate use in pregnancy. Between 2000 and 2009, the United States saw a five-fold increase in opiate use in pregnancy, coincident with an "epidemic" of opiate prescription misuse.[10–12]

There is little information available on the extent of substance use, other than tobacco, among pregnant women in low-income and middle-income countries. The overall prevalence of tobacco use in these countries is 2.6%, with some countries having much higher maternal rates– up to 15%.[13] While data on illicit substance use in pregnancy is lacking for most middle- and low-income countries, according to the World Health Organization, cannabis is the most common illicit drug worldwide, followed by amphetamine-type stimulants and opiates,[14] and, as such, they are likely to be used by women of reproductive age. The limited data available for Africa is from South Africa, and indicates that between 3.6 and 8.8% of pregnant women use illicit substances and 19.6% use alcohol.[15] The most commonly used illicit substances in South Africa include methamphetamine and cannabis.[16] Opiate use has also increased in places like Africa and Asia,[17] and is likely to become more prevalent in pregnancy.

Prenatal substance use can bring about several deleterious consequences for both mother and baby, as described in detail below. The concern for the impact of substances on the developing fetus can motivate some women to curb their drug and alcohol use during pregnancy.[18] In the only prospective study on prenatal substance use, 96% of women with heaving drinking, 78% of women with marijuana use, 73% of women with cocaine use, and 32% of cigarette smokers succeeded in achieving abstinence during pregnancy.[9] Offsetting the reduction in pregnancy-related use is the dramatic rise in substance use from 6 to 12 months postpartum.[9] The study showed relapse in 58% of abstinent smokers, 51% of abstinent women who used alcohol, 41% of abstinent women who used marijuana and 27% of abstinent women who used cocaine in the 3 months following delivery.[9] Thus, while the levels of abstinence in pregnancy may be high, the impact of this is diminished due to the high rates of relapse postpartum. Unfortunately, maternal relapse happens at a time of high childcare needs and when infant development is dependent on maternal bonding. It is also important to note that this was a study conducted in the United States and that the levels of abstinence may not be equivalent in other countries, especially middle- and low-income countries where women may encounter significant socioeconomic stressors, low levels of education, and limited available treatments for substance use.

As evidenced by these data, substance use in pregnancy is still a critical public health concern. The purpose of this review is to provide a brief overview of the pregnancy outcomes, neonatal and long-term developmental consequences of prenatal substance use, and current available treatments for pregnant women.

Adverse Effects of Substance Use in Pregnancy

Heavy alcohol use in pregnancy has been associated with a range of negative birth outcomes, including increased risks of miscarriage,[19] stillbirth and infant mortality,[20, 21] congenital anomalies,[22] low birthweight,[23] reduced gestational age,[24] preterm delivery,[25] and small-for-gestational age.[22, 26, 27] The evidence for low to moderate alcohol use in pregnancy has either been inconclusive[28] or shown no increased risk for these adverse pregnancy outcomes.[29] Alcohol use in pregnancy has the most well established adverse fetal health effects[30–32] and is associated with the development of fetal alcohol

spectrum disorders[33–35] and adverse neurodevelopmental outcomes.[36] In addition, prenatal drinking is associated with long-term effects, such as cognitive and behavioral challenges,[37, 38] adverse speech and language outcomes,[39] executive functioning deficits in children,[40] and psychosocial consequences in adulthood.[41]

Smoking during pregnancy exerts direct adverse effects on birth outcomes, including damage to the umbilical cord structure,[42] miscarriage,[43] increased risk for ectopic pregnancy,[44] low birthweight,[45–47] placental abruption,[45, 46, 48] preterm birth,[45, 49] and increased infant mortality.[45, 46, 48] Also of concern are the deleterious health effects of second-hand smoke on newborns, which include higher rates of respiratory and ear infections, sudden infant death syndrome, behavioral dysfunction and cognitive impairment.[50] Additionally, women who were smokers before pregnancy might stop breastfeeding early so that they can take up smoking again.[51]

Some pregnant women view cannabis use as harmless in pregnancy;[52] however, it has been linked with several deleterious effects, including preterm labor, low birthweight, small-for-gestational age, and admission to the neonatal intensive care unit.[53] Prenatal cannabis use has also been linked with adverse consequences for the growth of fetal and adolescent brains,[52] reduced attention and executive functioning skills, poorer academic achievement and more behavioral problems.[54] The adverse effects of marijuana are frequently observed with comorbid substance use, and are greatest in heavy users.

The extent of the adverse effects of cocaine use in pregnancy has been overestimated at times. However, there have been several large and thorough studies recently, which have all identified several risk factors associated with cocaine use during pregnancy, including premature rupture of membranes, placental abruption, preterm birth, low birthweight, and small for gestational age infants.[55, 56] There have been inconsistent reports on the long-term effects of prenatal cocaine exposure on language, motor, and cognitive development, with a few studies describing positive findings[57, 58] and some studies reporting very little or no effects.[59] This inconsistency is probably connected to the confounding effects of the postnatal environment, including unsteady and disordered home environments, dysfunctional parenting, and heavy maternal polysubstance use.[60–62] Similar to cocaine

use in pregnancy, methamphetamine use is linked with shorter gestational ages, lower birthweight,[63] fetal loss,[64] developmental and behavioral defects,[65] preeclampsia, gestational hypertension, and intrauterine fetal death.[66]

Opioid use in pregnancy is correlated with a greater risk of low birthweight, respiratory problems, third trimester bleeding, toxemia and mortality.[12, 67] Maternal opiate use is associated with an increased risk of *neonatal abstinence syndrome* (NAS), whereby opiate exposure in utero triggers a postnatal withdrawal syndrome.[12] Anywhere from 45% to 94% of infants exposed to opioids in utero, including methadone and buprenorphine, can be affected by NAS.[12] NAS results in substantial neonatal morbidity and increased healthcare utilization,[12, 67] and consists of an array of signs and symptoms, including irritability, feeding difficulties, tremors, hypertonia, emesis, loose stools, seizures, and respiratory distress.[68] Opioid exposure in pregnancy has also been associated with postnatal growth deficiency, microcephaly, neurobehavioral problems, and sudden infant death syndrome.[67] Cigarette smoking, which is very common in pregnant women with an opioid use disorder (77%–95%),[69, 70] may confound the effect of opioid use on poor pregnancy outcomes.

A significant point to take into account is that the undesirable consequences of prenatal substance use are confounded by the frequency of coexisting substance use and comorbid psychiatric illness.[71, 72] **Women with substance use disorders also frequently experience inadequate prenatal care, poor nutrition, chronic medical problems, poverty, and domestic violence.[73, 74] Furthermore, substance use in pregnancy may also result in an early dysfunctional maternal-infant relationship that can potentiate the negative effects of prenatal drug exposure.**[60, 61]

Treatment of Substance Use in Pregnancy

There are only a small number of effective therapies for substance use in pregnancy, which primarily involve behavioral counseling (see Table 1). Brief interventions,[75] in particular those that utilize motivational interviewing,[76, 77] have been shown to reduce prenatal alcohol use. A recent randomized trial utilizing a telephone-based brief intervention suggests that this method may achieve similar results to the in-person intervention method of

Table 1:
Description of Behavioral Interventions for Substance Use Disorders

Contingency management (CM)	Based on the principle of positive reinforcement as a means of operant conditioning to influence behavior change. The premise behind CM is to systematically use reinforcement techniques, usually monetary vouchers, to modify behavior in a positive and supportive manner. Originally used for the treatment of cocaine users, it has since been used for opioids, marijuana, cigarettes, alcohol, benzodiazepines, and other drugs.
Motivational interviewing (MI)	A patient-centered, collaborative and highly empathic counselling style for eliciting behavior change by helping clients to explore and resolve ambivalence. It draws from the transtheoretical model of change in order to improve treatment readiness and retention.
Cognitive Behavioral Therapy (CBT)	A psychotherapeutic treatment that uses an easy-to-learn set of strategies to help patients understand the situations that lead them to undesirable thoughts, feelings, or behaviors, to then avoid those situations when possible, and to deal more effectively with such situations when they occur. The goal of these strategies is to break old patterns of responding and replace them with new ones.

moderating prenatal drinking.[78] Some additional interventions to reduce prenatal drinking that have recently been described include screening via non-healthcare community workers,[79] counseling by midwives,[80] and multimedia and educational efforts aimed at improving awareness.[81]

As with alcohol, behavioral counseling is the main treatment for smoking cessation and relapse prevention in pregnant women. Unfortunately, psychotherapeutic interventions have had only moderate success.[82–85] Pharmacological treatments for smoking cessation have not been evaluated with respect to their safety and efficacy in pregnant and postpartum women.[82, 86] Randomized clinical trials with nicotine replacement therapy in pregnant women have demonstrated limited efficacy in increasing the rates of abstinence.[87–90] The most successful intervention for prenatal smoking cessation is *contingency management* (CM) with financial incentives,[91–93] which has also reportedly improved birth outcomes.[94]

Treatments specifically aimed at prenatal cannabis use are lacking. The current recommendation for lowering the use of cannabis in pregnancy includes the screening of pregnant women to increase the early identification of cannabis use.[52] *Motivational interviewing* (MI),[95, 96] *cognitive-behavioral therapy* (CBT),[95–99] and CM therapies have had some success in reducing marijuana use in women, but they have not been evaluated specifically with pregnant users. Thus, novel interventions that explicitly target cannabis use are vital, particularly given the current tendency towards marijuana legalization.

Existing evidence-based treatments for cocaine use in pregnancy include CBT, MI and CM.[100] As with smoking, CM is the intervention that shows most potential for treating cocaine-using pregnant women.[62] A randomized trial found that CM was associated with much longer duration of cocaine abstinence, higher number of cocaine-negative urine tests, and a greater proportion of documented abstinence when compared to community reinforcement approach and twelve-step facilitation.[101] Currently, there are no evidence-based pharmacological treatments for prenatal cocaine use. Nevertheless, a recent randomized, placebo-controlled trial supports the use of oral micronized progesterone as an intervention for postpartum cocaine use.[102] The study showed that women randomized to placebo had more self-reported cocaine use compared to women receiving micronized progesterone during the 12 weeks of the trial.[102] While these are preliminary findings and will require confirmation in a larger clinical trial, they show promise for the application of progesterone in postpartum women to reduce their cocaine use. Treatments for other stimulant use, such as methamphetamine, are limited. Research into *reinforcement-based therapy* (RBT) combined with a women-focused intervention among pregnant methamphetamine users reported a reduction in methamphetamine use over time.[103] However, there were no substantial distinctions between the intervention and control conditions,[103] not unlike another study using RBT to treat stimulant use in pregnancy.[104] RBT seems to have potential as an intervention for methamphetamine use but more research is required.

Methadone maintenance is the standard care for pregnant women with opiate use disorders.[105] Conversion from illicit opioid use to opioid maintenance therapy in a medically supervised setting decreases maternal and neonatal morbidity. Methadone maintenance offers greater relapse prevention with a steady opioid dosing regimen, reduces risk-taking behavior, enhances compliance with prenatal care, and leads to better neonatal outcomes.[106] On the other hand, medication-assisted withdrawal, that is detoxification by gradually reducing the dose of an opioid substitute medication, is associated with a high opioid relapse rate and higher fetal morbidity and mortality rates.[106] Buprenorphine has recently emerged as another potential therapy for opioid use in pregnancy. A randomized controlled trial that compared methadone and buprenorphine in pregnant opioid users showed that infants whose mothers received buprenorphine needed less treatment for NAS, substantially lower doses of morphine to treat NAS symptoms, and had shorter stays in hospital, compared to the infants of women given methadone.[107] Notably, buprenorphine had lower retention rates with flexibly delivered doses and low fixed doses compared to methadone.[108] However, buprenorphine and methadone are equally effective when given as fixed medium or high doses.[108] CM has likewise been reported to be effective in treating opioid use in pregnancy, by significantly increasing abstinence and treatment attendance compared to controls.[109] Thus, CM appears to be an important addition to methadone or buprenorphine treatment in pregnant women.

Breastfeeding and Postpartum Substance Use

Breastfeeding has the potential to be a useful tool for substance use in the postpartum period. Breastfeeding is the only available intervention shown to reduce NAS severity in opioid-exposed newborns.[110, 111] **Breastfeeding might also be protective for postpartum relapse. For example, among breastfeeding smokers, 10% stop breastfeeding because of smoking, and over half of recent or current smokers reported that smoking affected their infant feeding decision.[112] In addition, non-current smokers are more likely to initiate and continue breastfeeding compared to current smokers.[113, 114] Therefore, the promotion of breastfeeding might prevent or delay postpartum relapse.**

While studies evaluating the potential role of breastfeeding as an intervention for substance use postpartum are limited, the rationale for such interventions is clear. Lactation reduces the HPA response to physical stress.[115] A behavior that promotes relaxation and reduces stress would be helpful to women with substance use disorders since psychosocial stress increases cravings.[116] While hormones released during lactation may mediate stress reduction, such hormones have other properties that may help women cope with addiction. Considerable attention has been dedicated to oxytocin, a hormone released during delivery and lactation. Oxytocin administration is under investigation for treatment of drug and alcohol use disorders.[116–118] In addition, lactation is positively associated with cognitive and motor development in the infant.[119] It is well known that stable attachment among children increases resiliency and protects against the development of addiction later in life.[120, 121] Thus, an intervention that promotes lactation and intimacy through skin-to-skin contact may enhance stable attachment, and have the intergenerational benefit of protecting offspring from the development of addictive and other problematic behaviors.[120, 122, 123]

Conclusions

Substance use in pregnancy remains a significant public health problem, which can lead to several harmful maternal and neonatal outcomes. Which drug is being used and the degree of use, as well as the point of exposure, all influence the effects of drug use in pregnancy. In addition to the direct effects of drug exposure in utero, several other variables are associated with deleterious maternal and infant consequences, including psychiatric comorbidity, polysubstance use, limited prenatal care, environmental stressors and disrupted parental care. In conjunction, these factors can negatively influence pregnancy and infant outcomes, and should be taken in to account when developing interventions for prenatal substance use treatments. **Many of the health problems associated with substance use in the prenatal period could be avoided given effective and well-timed medical care or intervention. Empirically-driven interventions for**

prenatal substance are needed. While there are few treatment options for substance use in pregnancy, CM seems to show the greatest promise as an effective therapy for the substances in which it has been studied. Future research needs to focus on developing tailored, safe, and acceptable treatments that can capitalize on pregnancy as a "teachable" moment that can motivate women to adopt risk-reducing health behaviors.[124–127] ꙮ

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L003382

Multiple-Choice Questions

73. According to the lesson, what percentage of pregnant women drink alcohol?

   A. 8.5%

   B. 14%

   C. Less than 1%

   D. 6%

74. All of the following are outcomes of heavy alcohol use in pregnancy, *except*:

   A. miscarriage.

   B. high birthweight.

   C. preterm delivery.

   D. infant mortality.

75. What are some common co-occurring problems from pregnant women suffering from substance abuse?

   A. Poor nutrition

   B. Poverty

   C. Domestic violence

   D. All of the above

76. What is the main treatment for smoking cessation in pregnant women?

   A. Family therapy

   B. Antidepressant medication

   C. Nicotine patches or gum

   D. Behavioral counseling

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Best Practices in CME

Substance Use During Pregnancy

By Ariadna Forray, MD

ID#: L003382

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

This lesson reviews how pervasively substance use disorders can affect pregnant women. By reviewing the different types of substances that are most frequently used by women, the authors explore the different ways this can impact a fetus during pregnancy. Looking at co-occurring mental disorders, as well as life circumstances, the authors paint a full picture of the challenges clinicians will face when working with pregnant women with substance use disorders. Treatment of these issues can be difficult, and research has only begun to explore the effects different factors can have on a woman's chance of recovery.

Key Point 1: Prevalence of Fetal Exposure to Substances

Over one million fetuses are exposed to illicit drugs, alcohol, and tobacco every year. Over 380,000 offspring exposed to illicit substances, over 550,000 exposed to alcohol and over one million exposed to tobacco in utero.

Key Point 2: Emotional Sequela

Pregnant women with substance use disorders also frequently cope with other negative life circumstances. Poverty, domestic violence, poor nutrition, chronic medical conditions, and poor access to healthcare are common issues faced by pregnant women with substance use disorders.

Key Point 3: Breastfeeding & Relapse Prevention

Breastfeeding may aid in the cessation of behaviors and relapse prevention. Studies show that among breastfeeding smokers, 10% stop breastfeeding because of smoking, and over half of recent or current smokers reported that smoking affected their infant feeding decision.

Key Point 4: Necessity of Early Intervention in Pregnant Women

Many of the health problems associated with substance use in the prenatal period could be avoided given effective and well-timed medical care or intervention. Research to provide evidence-based treatments for substance use disorders in pregnant women are needed.

Notes

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Knowledge Transfer in the Field of Parental Mental Illness: Objectives, Effective Strategies, Indicators of Success, and Sustainability

Camilla Lauritzen, PhD; and Charlotte Reedtz, PhD

KEYWORDS: Health system improvement • Children of mentally ill parents • Effective strategies • Sustainability

LEARNING OBJECTIVES: Readers will review the need and complexities of establishing, implementing, and sustaining interventions to reduce the transference of mental illness from parents suffering from mental illness to their children. This lesson explores aspects of knowledge transfer, indicators of success, and continuance.

ABSTRACT:

Background: Mental health problems are often transmitted from one generation to the next. However, transferring knowledge about interventions that reduce intergenerational transmission of disease to the field of parental mental illness has been very difficult. One of the most critical issues in mental health services research is the gap between what is generally known about effective treatment and what is provided to consumers in routine care.

Discussion: In this article, we discuss several aspects of knowledge transfer in the field of parental mental illness. Effective strategies and implementation prerequisites are explored, and we also discuss indicators of success and sustainability.

Summary: Altogether, this article presents a rationale for the importance of preventive strategies for children of mentally ill parents. Furthermore, the discussion shows how complex it is to change clinical practice.

COMPETENCY AREAS: This lesson aims to fill the gap of knowledge in the care of parents with mental illness to help mitigate the transference of psychiatric disorders to their children. This authors highlight the necessity of working in interdisciplinary teams to share information, the need for clinicians to take preventative steps to help break the cycle of mental illness that is transferred from parent to child, and the challenges to systemically realize these goals in clinical practice.

Background

Knowledge transfer can be defined as: The process which one unit – for example; an individual, a group, a department or an organization – is affected by the experience of another.[1] It is important to highlight that providing information, presenting facts, arranging informative courses or even giving lectures is not the same as knowledge transfer. This is because knowledge alone is not necessarily sufficient in order to create behavior change. In essence, knowledge transfer is about facilitating behavior change. One way of explaining knowledge transfer is to regard it as the process of organizations seeking to improve performance by implementing a new practice.[1, 2]

How is knowledge transferred from one unit or organization to another? There are several factors that can facilitate or impede knowledge transfer in organizations and it is definitely possible to design organizations and procedures to promote knowledge transfer.[1, 2] This is, however, a very complex area, consisting of many important mechanisms. The literature is extensive on this field, and we will discuss the most important mechanisms of knowledge transfer later in this article, but for now let's just agree that there are many issues to address if you want to understand the mechanisms of knowledge transfer.

The Field of Parental Mental Illness:

Many studies have documented that mental illness is very common.[3] Mental illness is defined as a psychological pattern, potentially reflected in behavior, that is generally associated with distress or disability and is not considered part of normal development.[4] According to the DSM-IV criteria, the term mental disorder refers to a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual, is associated with present distress or disability and represents a manifestation of a behavioral, psychological, or biological dysfunction in the individual. The most common mental health problems are anxiety, depression and substance abuse issues.[5] In a 2009 report on mental illness in Norway, The Norwegian Institute of Public Health (2009) estimated that up to 50% of the population will suffer from mental health problems at some point during their lifetime.[5]

Adults with mental health problems are not less likely to be parents then the rest of the population.[6] Several international studies the past two decades have indicated that children with mentally ill parents are at risk of developing mental health problems themselves.[7, 8, 9] Parental mental illness is considered a powerful risk-factor, with a potential of serious impact for the children. For instance: parents with depression have more difficulties in interaction with their children, are more intrusive, less involved and less responsive.[10, 11, 12]

More than one third of these children develop serious and long-lasting problems. Early in life, these children run a higher risk of abuse and neglect, depression, eating disorders, conduct problems and academic failure. Later in life, they are at a higher risk of depression, anxiety disorders, substance abuse, eating problems and personality disorders.[13, 14, 15]

Maternal symptoms of anxiety and depression increased the risk of emotional and disruptive problem behaviors in children as early as 18 months of age, according to new research findings from the Norwegian Institute of Public Health. And these problems are often found to be long lasting.[16]

It is especially when parental mental illness is present during the early years of life that it triggers dys-regulated emotion patterns, negative emotionality and insecure attachment. A lot of documentation exists on the serious effects parental mental illness may have on the early developmental stages of a child's life.[17-22] It is safe to say that early intervention is essential to counteract permanent damage to the child's developmental path.

Parental mental illness may interrupt the neurological development in offspring.[23, 24] Since the brain is not fully developed when we are born, the experiences a child has growing up will have direct effect on the development of the brain.[23, 24] Children of mentally ill parents are in many cases exposed to traumatic childhood experiences, for example: they can be witnesses to violence, or they may have been subject to abuse or neglect. This is commonly referred to as developmental traumas. Developmental traumas result from growing up in a context of ongoing danger, maltreatment, unpredictability, and/or neglect. Developmental traumas tend to surface as several disorders, i.e., regulatory disorder during infancy, attachment disorders, hyperkinetic conduct disorder at school age, or combined conduct and emotional disorders during adolescence.[23, 24] **Children**

that live under stressful conditions over time, will produce a lot of stress hormones and the child is in a way becoming programmed into a state of constant emergency preparedness. **The child's cognitive resources are tied up in being in a state of emergency, and this delays and impairs the child's development in other areas.[23, 24]**

Regulatory competence is a key concept. Emotional regulation is developed early in life in interaction with caregivers. **Emotional regulation is a complex process involving: the subjective experience (feelings), cognitive responses (thoughts), physiological responses (for example heart rate or hormonal activity), and behavior (such as bodily actions or expressions).[25]** Children who have been neglected or abused have been found to have a dysfunctional self-regulatory competence.[23]

The impact parental mental illness may have on offspring is commonly ignored within the adult mental health services,[26] even though there is thorough documentation that Parental mental illness is a powerful risk factor for children. The objective of including a focus on the patient's children is linked to prevention, because there are measures that can be taken to counteract the risk, for instance by implementing a prevention perspective in adult mental health services. There is a substantial amount of research documenting that teaching parents positive parenting strategies to promote children's self-confidence, pro-social behaviors, problem-solving skills and academic success reduces the risk for those children.[27, 28] **There is also growing evidence to support the idea that strengthening protective factors for children of mentally ill parents may reduce the incidence or prevalence of some mental disorders.[4] There are several well-known protective factors for children of mentally ill parents, and they are commonly divided in three categories: family related factors (such as parental participation in the child's life, sensitive upbringing strategies and consistent child-rearing approaches), individual factors (gender, self-esteem, intellectual capacity, social skills), and structural factors (positive school environment, social network, socio-economic status).[21]**

The prevention objective is threefold. First of all it's about preventing children from developing poor regulatory competence, insecure and disorganized attachment.[23]

It also involves preventing added burden to the parents disease, because research has documented that treatment alone is not as effective as when it is combined with family focused strategies.[29] And thirdly, and hopefully as a result of this; preventing mental illness from being transmitted from one generation to the next.[10]

Discussion

There are several important aspects to discuss in terms of successfully implementing a child perspective within adult mental health services. Prevention work is generally difficult, and so is implementation work.

Effective Strategies:

When we discuss preventive strategies and early intervention approaches, it is important to investigate what kind of evidence we have that prevention is effective. Durlak and colleagues conducted a meta-analysis in 1997, demonstrating that programs to prevent mental disorders can be effective for children.[30] In 2002, Jané-Llopis found that effects of prevention programs are stable over time, and are effective for populations with different levels of risk.[31] So generally there is evidence to support the use of preventive programs.

What about the programs specifically developed for the field of parental mental illness? Many of the strategies within preventive interventions involve aspects of parent training. The idea is that parent training programs can help families and children to regulate the child's thoughts, feelings and behavior.[32] Within the field of parenting there are several programs that have an extensive evidence base.[33] Parenting programs may be used to promote good mental health in children also in the field of parental mental illness.[34] Parent training programs is a good option for some of the families affected by parental mental illness, however depending on the diagnosis and the severity of the situation. Furthermore, these programs are used by a growing number of local communities, and may be easier to get access to than programs that are more specifically designed for parental mental illness issues.

There are also some programs that are more specifically designed to target families affected by parental mental illness. In 2012, a meta-analysis was published. The authors assessed the evidence in terms of effectiveness of the preventive interventions in decreasing the

risk of mental disorders in the offspring of mentally ill parents.

The conclusion in this meta-analysis is that the evidence indicated that such interventions may be effective and that different approaches to treatment of the families may be equally effective.[35] However, the results from the studies reported in the meta-analysis mainly consisted of mothers with affective disorders and depression, and the results may therefore be less applicable to parents with other mental disorders and to fathers. Additionally, several studies included were of questionable standards and this may have led to an overestimate of the effects.[35] The authors do however point to the need for further studies of sufficient size and high methodological quality.

In 2012, a review of intervention programs for children whose parents have a mental illness was published, providing an overview of available interventions. The authors of this review divided the interventions in three groups:

1. **Family intervention programs.**

2. **Peer-support programs for children.**

3. **Online interventions for children/adolescents whose parents have a mental illness.**

The most common component in the programs was provision of psychosocial education about mental illness. Only some of the interventions had been evaluated, and very few had been evaluated in Randomized Controlled Trials.

The authors concluded that more evaluations are needed in this field, and particularly studies that incorporate validated outcome measures.[36]

So in the field of parental mental illness, what would be effective strategies for knowledge transfer? An effective strategy should take into account the fact that parental mental illness has serious consequences for children and that we can prevent the transgenerational transmission of mental illness by preventive interventions.

Furthermore, there are several existing interventions with good evidence of effect that can be used to train parents in better parenting strategies; e.g., the Incredible Years program or the PMTO (parent management training Oregon) intervention. There is a problem when policy makers and other agencies decide to disseminate programs

that have no documented effects. In worst case scenarios, programs may prove to have negative effects. And, even if the situation should be that the strategy chosen had no effects–it would be a major waste of resources. This is why programs that have been evaluated and found to be effective should be priority number one, if such documentation exists. When planning effective strategies in this context, evidence based programs are preferable to interventions without evidence of effect. However, in order for a strategy to be effective, the implementation aspect has to be a part of the equation.

Implementation of Effective Strategies:

Knowledge transfer can be challenging and one perspective that may be useful in addressing these challenges is to be found in the substantial body of implementation literature. The essence of implementation is behavior change. Implementation is defined as *a specified set of activities designed to put into practice an activity or program of known dimensions.*[37]

Currently, little is known about the processes required to effectively implement evidence-based programs on an international scale. Rigorous research to support the implementation activities that are being used is even scarcer. A major goal in the Implementation Research area is to help establish an evidence base for the implementation processes.[37]

Implementation may involve different connotations for different people. When referring to implementation, different agents refer to a variety of contrasting activities and strategies; and the strategies they refer to represent varied depth and dedication.[38] **The differing views of implementation may be categorized as degrees of implementation in the following way. The first degree is paper implementation. This refers to putting new policies and procedures into place; e.g. legislation, commission documents and guidelines. However, changing policies and procedures does not change practice in itself.**

The second degree is called Process implementation. This means incorporating new procedures into an organization; i.e. providing new guidelines and supervision, and changing reporting forms, among other things. However, the "mechanism" to change may not exist because this strategy does not incorporate any tools or specific intervention to guide the change in

behavior. The highest degree of implementation is commonly referred to as performance implementation. This is the most extensive degree of implementation, meaning that it provides content and tools to practitioners so that new procedures and processes have functional components for change. According to the implementation research literature, performance degree implementation strategies are more likely to be successful than the other two degrees of implementation.[38]

There are several core components that work together in any attempt to implement and sustain effective innovations.[39] These core components are; decision support data system (for instance organizational fidelity measures), a facilitative administration that provides leadership and support in the process, system intervention to ensure the availability of financial, organizational and human resources, recruitment and selection, pre-service training, consultation and coaching, and finally staff performance evaluations. The integrated and compensatory nature of the core components embodies the perspective that organizations are dynamic, and there will be variations in the relative contributions of each component to the overall outcomes. However, if the core components are not taken into account and assessed in implementation projects, the result may be unsuccessful implementation processes.[39] Even though there is some evidence to support the importance of the core components,[39] more rigorous implementation research should be conducted to extend the evidence base of core implementation components.

Behavior Change:

Implementation of new routines involves behavior change. Many strongly believe that increasing knowledge and changing attitudes also change people's behavior. This is linked to a belief that awareness campaigns, education and a general focus on a subject, will cause behavior change in people. In the study of changing clinical practice to safeguard children of mentally ill parents, this view implies that information and courses for health professionals should have the potential to change clinical practice. Within health promotion campaigns, this has been a particularly common strategy,[40] for instance campaigns to encourage people to stop smoking. The no-smoking strategy has been effective because the strategy has been multi-layered; from restricting the availability, banning smoking in public areas to strategies to change attitudes, and strategies to help people gain control over their behavior.

The point is: in order for a strategy to improve the situation for families affected with parental mental illness, the strategy must incorporate more than information about risk-factors. Behavior change is complicated. This implies that is not sufficient to simply point out why something should change, how the changes are to come about must also be determined. There is no reason to expect that positive general attitudes to improved services for children of mentally ill – or even increased knowledge about the risk of these children–automatically will change clinical practice. There is no theoretical or empirical foundation to expect specific skills and behaviors to arise from a general dissemination of knowledge and positive attitudes.

Where Should We Begin?

It is not of indifference where a process of knowledge transfer or behavior change should begin. A model which was developed by Maybery and Reupert in 2009 was designed as a hierarchy of points of intervention to affect workforce change, because it is unlikely that higher level activities can be successful unless the lower levels of the hierarchy already exists in the organization.[41]

The lowest level represents the importance of the policies within an organization, for example guidelines. Strategies to change practice have to be embedded in the organization, and the management has to be on board with the aims to change.

The next level of the hierarchy consists of issues relating to the workforce for example workers' attitudes, skills and knowledge. The most important areas for workers to develop in this context include reporting systems, assessment, referral procedures and psychoeducation in regard to the service user. The groundwork of stage one and two will then enable the workers to engage with the service user.

Level three of the hierarchy represents the barriers families themselves bring in. Parents may not know the consequences their illness has on their children, or they may be reluctant to discuss this with others. Parents may have fears that discussing their insecurity and problems in childrearing may lead health personnel to worry about the quality of care their children receive, and consequently

that others will report them to the Child Protection authorities. Once organizational anchoring has been done and the workforce has been trained to engage with the clients in a family oriented perspective, only then is it realistic to achieve a clinical practice that incorporates the parental mental illness aspect.

You have to have the bottom levels first in order to achieve the top level. This means that in the process of changing clinical practice, one should always start with initial groundwork such as; creating a detailed protocol that accounts for time and resources within the organization, assessing organizational needs, addressing requirements from the health authorities and so on. According to the model, the resistance and unwillingness the service users may have to discuss their children will be less prevalent when organizational issues and workforce related problems have been addressed.

We did a slight modification of the model to adapt the model to a Norwegian context.[42] We believe that an infinite amount of resources and efforts at the lower level will not allow movement upwards, because the movement is hindered by a contextual dimension. We therefore added a contextual level to the model, to incorporate these challenges. The added dimension encompasses two important aspects that are external conditions, but with a potential large impact on the movement from one stage to the next in the model. The first aspect is (1) the organization of mental health care services, Services for adults and services for children are two very different organizations and not necessarily co-operating. The second aspect is (2) the geographical context in which the mental health care services are provided. Sometimes the home-community is very far away from the hospital the adult is admitted to. This makes it difficult, if not impossible, to bring in the children to visit and receive preventive interventions within adult mental health services. A possible solution to this could be to offer interventions in the local communities instead of the hospitals. However, since the workforce at the hospitals have better knowledge of the mental health issues of the parents; perhaps telecommunication solutions could be explored?

Indicators of Success:

Sometimes it is difficult to know for certain that the strategies chosen have been effective. What we think may be the case is not necessarily accurate. Clinicians or managers may have a hunch that what is done within the clinic to support children of mentally ill is good, based on perhaps one person's *very* dedicated work in the area. It does not always mean that *everyone* is doing dedicated work. We need reliable ways of assessing success.

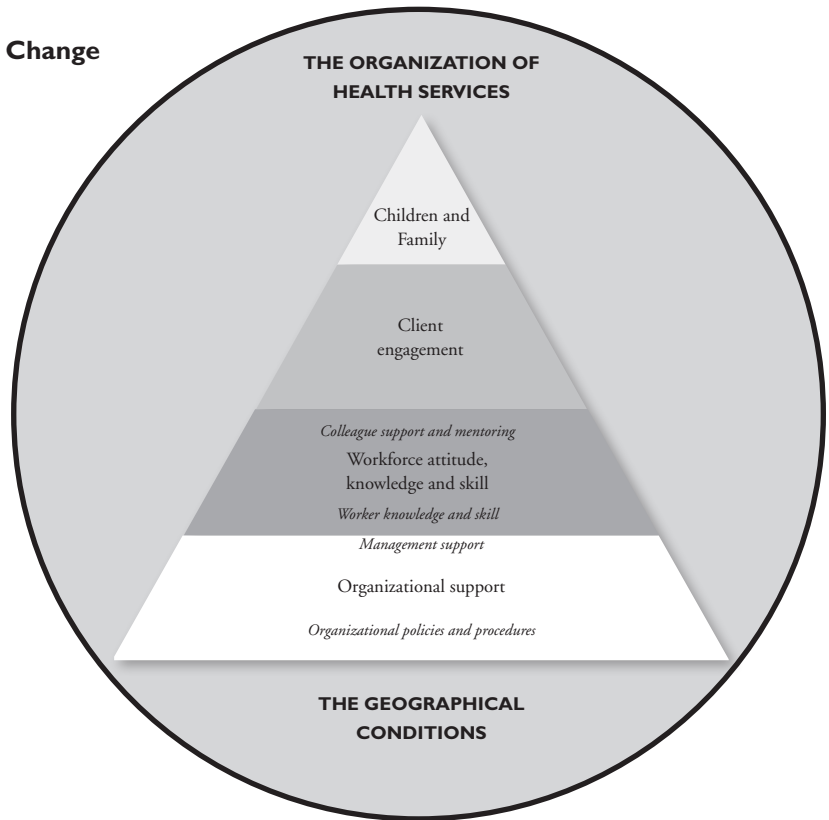In terms of measuring success, we are talking about two different processes.

We're talking about evaluating the effects of the interventions and in that sense monitoring if the strategy is successful (levels 3 and 4 in the hierarchy, Figure 1). We're also talking about monitoring the implementation process and keeping an eye on the process of change at all times (levels 1 and 2 in the hierarchy, Figure 1).

Indicators of success in terms of client engagement and services for children and families (level 3 and 4, Figure 1) can be detected by studying the effects of the interventions. This implies that in terms of the interventions one chooses to apply in the field of parental mental illness, one way of measuring success is to look at the outcomes for children and families. To look for indicators of success you have to look into the evaluations on the intervention's effect on parents and children, in efficacy studies, effectiveness studies or other approaches to evaluation. Good outcomes for children is in itself an indicator of a successful approach. Monitoring the outcomes for children is important in addition to monitoring the process of implementation of the intervention in real life. Fidelity is of course also very important. **In the field of program evaluation, the term fidelity denotes how closely a set of procedures were implemented as they were supposed to have been.** For example, it's difficult to draw conclusions from a study about effective strategies in the field of parental mental illness if the practitioners are not able or willing to follow the procedures they received in training. Subsequently, higher fidelity is correlated with better outcomes, and therefore a significant factor in the assessment of success indicators. Studies that used fidelity scales have found better outcomes for consumers when services adhere closely to an approach with specified critical components and standards.[43]

The other approach to measuring success is linked to studying the process of implementation, and documenting activities related to level 1 and 2 in the hierarchy (see Figure 1). In Implementation research – measuring processes of change is crucial in order to keep track of the

Figure 1:
Adapted Hierarchy to Affect Workplace Change

Adapted hierarchy to affect workforce change (Maybery & Reupert 2009, Adapted by Lauritzen & Reedtz).

THE ORGANIZATION OF
HEALTH SERVICES

Children and
Family

Client
engagement

Colleague support and mentoring
Workforce attitude,
knowledge and skill
Worker knowledge and skill
Management support
Organizational support
Organizational policies and procedures

THE GEOGRAPHICAL
CONDITIONS

indicators of success, and one aspect that is important to address is readiness to change. Organizational readiness to change is considered a critical precursor to achieve successful implementation of complex changes in healthcare settings. This implies that the implementation strategies should encompass activities to create motivation to change. On-going assessment of organizational readiness is very important in order to be successful in any attempts to change.

Furthermore, to keep track of the process it is important to evaluate the core variables that you want to change in the implementation strategy. In our study, these have been linked to knowledge, attitudes, collaborative routines and clinical practice related to families with parental mental illness. The road to success may not be as straight forward as we imagine when we set up our protocols and project plans, which is why we need to monitor the process. We need to be aware of what is going on along the way.

An example of a tool that can be used to monitor the process of change is measuring collective efficacy.

The term collective efficacy refers to individual group members' perceptions of the capability of the group to achieve specific goals.[44] In therapeutic organizations it represents the practitioners' and the leaders' perceptions as a whole that their agency is capable of creating positive outcomes for the children.

The readiness of an organization for successful implementation of evidence-based practices may be predicted in part by an organization's level of collective efficacy.[45] This means that a valid measure of collective efficacy in services may be particularly interesting in implementation research. However, as a self-report measure of capability to create positive outcomes for patients and families the tool is subjective and therefore limited. A solution to this limitation could be to include more concrete measures such as case load.

Sustainability:

If the implementation process is successful, and we have successfully transferred knowledge about parental mental illness and about effective interventions to

achieve the objectives of better outcomes for parents and children; how do we get it to stick? In terms of new-practice glue, the term to discuss this is sustainability. Sustainability addresses the issue of how the new practice, the transferred knowledge, is to survive in the every-day practice.[46]

Finances are also a big issue, as many preventive interventions fail to become sustainable because insufficient resources are provided. Cost-benefit analyses play an important role in the planning and decision making process of implementation projects, and sustainability issues need to be a part of the analyses.

The goal with sustainability is the long term survival and continued effectiveness of the implementation site in the context of a changing world. A review article published in 2012 by Stirman and colleagues provides an overview of the current state of the research literature on the sustainment of interventions.[46] One finding in this review was that partial sustainability was very common, meaning that elements of the implementation had survived, but not necessarily all elements that make up a program package.

The studies that reported on full sustainability were few and did not include long-term reports of post-implementation outcomes. Follow up measures to monitor sustainability is necessary and preferably more than just one-year follow up studies.

The conclusion was that the body of literature on sustainability was fragmented and underdeveloped.[46] To advance what is known about sustainability will require time, resources and funding. Appropriate planning assessment and allocation of funds would result in much better understanding of why and how some interventions last and others do not.

There are of course a lot of challenges related to sustaining interventions in the field of practice. The sustainability strategies should encompass strategic support within the organization. The success and sustainability of evidence based practices can be substantially influenced by the quality of organizational support systems for the program and leadership support.

It is important to retain an ongoing capacity for sustaining the interventions.

Implementation projects need to be properly anchored in the organization. The management must actively support the implementation of a new practice,

and this should be reflected in the policies within an organization, such as guidelines, service statements, protocols and interagency guidelines. Sufficient human resources and time to take on the new tasks must be allocated. Additionally, the managers must emphasize that the new practice is relevant and worth taking on. Otherwise, the hope of establishing the new routines within practice as usual is at risk. There must be ongoing recruitment of practitioners to carry out the interventions, which implies resource allocations. Sustaining interventions is reliant on core implementation personnel, but also on-going routine evaluations to monitor the implementation activities.

Conclusion

To sum up, where do we stand in general on knowledge transfer in the field of parental mental illness? We know something about effective strategies, we have well defined objectives, we have a few effective interventions, and especially interventions that target parenting behavior have a good evidence base. The evidence base on interventions specifically designed to address families affected by parental mental illness is growing, but more studies should be conducted in this area. We have models to help us understand behavior change and complex implementation issues. We even have ways to measure indicators of success, and we know something about how to create sustainable practices. The question is perhaps: do we have the patience? We need to recognize that knowledge transfer or implementation work is time consuming.

On the one hand; Researchers need to acknowledge the fact that they might have to work closer with the field of practice, and perhaps invest in longer time perspectives than traditional research projects. On the other hand; practitioners need to commit to the project protocols and invest time in adopting the new routines. If we pull together we can perhaps succeed in the endeavor to bridge the gap between research and practice.

Incorporating effective strategies in adult mental health services can potentially prevent parental mental illness being transmitted from one generation to the next.

It is therefore important for both researchers and practitioners to remember why the extensive strategies to change clinical practice are important. For the children and families who may benefit from the changes, it may mean a world of difference.

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L003383

Multiple-Choice Questions

77. Which one of the following statements is correct regarding parental mental illness?

    A. Parental mental illness may interrupt the neurological development in offspring.

    B. Adults with mental health problems are not less likely to be parents than the rest of the population.

    C. Studies demonstrate that children of parents with mental illness are at risk of developing mental health problems themselves.

    D. All of the above.

78. According to the lesson, what does sustainability refer to in regard to parental mental illness?

    A. Sustainability denotes how closely set procedures are implemented as originally intended.

    B. Sustainability is the implementation of new routine.

    C. The goal of sustainability is the long-term survival and continued effectiveness of the implementation site in the context of a changing world.

    D. None of the above.

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Best Practices in CME

Knowledge Transfer in the Field of Parental Mental Illness: Objectives, Effective Strategies, Indicators of Success, and Sustainability

By Camilla Lauritzen, PhD; and Charlotte Reedtz, PhD

ID#: L003383

This valuable take-home reference translates evidence-based, continuing medical education research and theory, acquired from reading the associated CME lesson, into a step-wise approach that reviews key learning points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Mental health problems are often transmitted from one generation to the next. However, transferring knowledge about interventions that reduce intergenerational transmission of disease to the field of parental mental illness has been very difficult. In this lesson, the authors discuss several aspects of knowledge transfer in the field of parental mental illness and a rationale for the importance of preventive strategies for children of mentally ill parents.

Key Point 1: Background of Parental Mental Illness

Parental mental illness is considered a powerful risk-factor, with a potential of serious impact for the children.

Key Point 2: Sequelae of Parental Mental Illness in Children

Parental mental illness present during the early years of children's lives can trigger dysregulated emotional patterns, negative emotionality, and insecure attachment. Developmental traumas tend to manifest in several disorders such as regulatory disorder during infancy, attachment disorders, hyperkinetic conduct disorder at school, or combined conduct and emotional disorders during adolescence.

Key Point 3: Prevention of Mental Illness and Protective Factors

Helping children of parents with mental illness achieve self-regulatory competence is essential. Strengthening protective factors, (i.e., family related factors, individual factors, and structural factors) in these children will help mitigate the development of mental illness.

Key Point 4: Implementation of Strategies

The transfer of knowledge to address the challenges in preventing parental mental illness from being passed to children key. Studies indicate the need for further research to ascertain whether promising results consisting of mothers with affective disorders and depression can be applied to parents with other mental disorders and fathers. Nonetheless, family intervention programs, peer-support programs for children, and online intervention for children/adolescents whose parents have a mental illness are effective.

Key Point 5: Sustainability is Key

Once clinicians and policy makers decide upon a treatment program, not only is implementation key, but sustainability—which addresses how the new practice, and

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the transferred knowledge is to survive and be maintained in daily practice, is essential. The goal of sustainability is the long-term survival and continued effectiveness of the implementation site in the context of a changing world.