CATEGORY 1
AMA PRA
Credit Hours

CME

VOLUME
38

Directions in Psychiatry

VOLUME 38 * LESSONS 1 – 20 IN THIS VOLUME

Directions in Psychiatry

Program Advisory Board

hatherleigh

www.DirectionsinPsychiatry.com

The Hatherleigh Company, Ltd
62545 State Highway 10 • Hobart, NY 13788

Accreditation Statement

The Hatherleigh Company, Ltd. designates this activity for a minimum 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.

The 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.

Learning Objectives Evaluation Form

Directions in Psychiatry, Vol. 38

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 be able to:

CME Lesson 1: Cannabis: Medicine or Mayhem? Part I: History and Epidemiology

___ summarize the history, trends, and prevalence of marijuana use and *marijuana use disorder* (MUD) in the United States.

___ describe epidemiological trends that influence prevalence rates.

CME Lesson 2: Opioid Use Disorder: A Review of Medication-Assisted Treatment and Psychosocial Programs

___ recognize the prevalence and epidemic of *opioid use disorder* (OUD) and its increasingly deadly nature.

___ identify approved medications for opioid use disorder to administer effective treatment.

CME Lesson 3: Food Addiction

___ identify the neuroscientific and phenomenological components of food addiction as it relates to substance use disorders and eating disorders.

___ examine treatment strategies for patients with food addiction to select the appropriate one.

CME Lesson 4: Core Clinical and Ethical Considerations for Psychiatrists Treating Transgender Persons and Persons With Intersex Conditions

___ review ethical problems that may arise in the treatment of transgender and intersex patients and optimal options for resolving them.

___ identify current theories regarding optimal approaches to infants born with intersex conditions.

CME Lesson 5: A Postal Survey of Doctors' Attitudes to Becoming Mentally Ill

___ recognize the most prominent barriers to seeking care for and reporting mental illness and thus become more vigilant to overcome these barriers.

___ gain knowledge that will help them foster an environment that does not stigmatize peers for seeking help.

CME Lesson 6: The Mentally Disordered Offender's Path Within the California Correctional System: California's Mentally Disordered Offender Act

___ assess the applicability of the *Mentally Disordered Offender* (MDO) Act to individual inmate/patients.

___ formulate opinions regarding the applicability of the six statutory criteria for MDO status to individual inmate/patients.

CME Lesson 7: The Role of Long-Acting Injectable Antipsychotics in Schizophrenia

___ describe to a patient the benefits of a *long-acting injectable* (LAI) antipsychotic over its oral formulation.

___ identify patients who should be prioritized for treatment with an LAI.

CME Lesson 8: Competing With Learned Fear: Implications of Fear Extinction for Clinical Intervention

___ identify the signs and symptoms of *posttraumatic stress disorder* (PTSD).

___ delineate the fear-learning mechanisms underlying trauma-, stressor-, and anxiety-related disorders.

CME Lesson 9: Internet and Gaming Disorder and Associated Changes in the Brain

___ review recent evidence of *internet gaming disorder* (IGD) on brain imaging studies.

___ describe how structural and functional brain imaging studies—including studies of grey matter volume, and white matter density, functional connectivity, executive function, reward and craving—can be used to identify IGD comorbidity with other psychiatric disorders.

CME Lesson 10: Vitamins, Minerals, and Herbs: Their Effects on Neurocognitive Disorders

___ describe *neurocognitive disorders* (NCDs) and identify their neurocognitive domains.

___ identify the clinical characteristics of *Alzheimer's disease* (AD) and explain current theories about its pathophysiology.

Learning Objectives Evaluation Form

Directions in Psychiatry, Vol. 38 (cont.)

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CME Lesson 11: Qualitative Investigation of Effects of 9/11 Attacks on Individuals Working in or Near the World Trade Center

___ describe the current research of the psychosocial effects of the attack on the *World Trade Center* (WTC) in New York City on September 11, 2001 (9/11).

___ describe how this disaster was experienced by employees of companies located in or near the WTC during the attack.

CME Lesson 12: Assessing PTSD in Ethnic and Racial Minorities: Trauma and Racial Trauma

___ recognize various factors that contribute to an increased risk for *posttraumatic stress disorder* (PTSD) in people of color.

___ identify underrecognized race-based traumatic experiences.

CME Lesson 13: Cannabis: Medicine or Mayhem? Part II: Neurobiology and Health Impact of Marijuana

___ demonstrate understanding of the endocannabinoid system, and its functional role in both central and peripheral systems.

___ differentiate the function of *Cannabinoid 1* (CB-1) from *Cannabinoid 2* (CB-2) receptors.

CME Lesson 14: Management of Treatment-Resistant Depression in Late Life

___ comprehend the prevalence and burden of depression and treatment-resistant depression in the geriatric population.

___ appropriately assess for the diagnostic variables related to *treatment-resistant depression* (TRD) in geriatric patients.

CME Lesson 15: Care of Pregnant Woman with Severe Mental Illness

___ recognize the importance of a multidisciplinary approach to the care of women with severe mental illness during the perinatal period.

___ define and describe treatment strategies for the various types of psychiatric disorders seen in pregnant women.

CME Lesson 16: Navigating Through Psychiatric Disorders Due to Another Medical Condition, Part I: Overview

___ delineate psychiatric symptoms associated with disorders in specific body systems.

___ identify warning signs that a medical condition may underlie the presenting psychiatric symptoms.

CME Lesson 17: Navigating Through Psychiatric Disorders Due to Another Medical Condition, Part 2: Cases

___ delineate psychiatric symptoms associated with disorders in specific body systems.

___ identify warning signs that a medical condition may underlie the presenting psychiatric symptoms.

CME Lesson 18: Are You Dreaming? Cognitive-Behavioral Therapy for Insomnia

___ list and define the criteria for identifying insomnia provided in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).

___ review the benefits of *cognitive-behavioral therapy* (CBT) for insomnia.

CME Lesson 19: Transgender Care: Health Care Disparities and Physician Attitudes

___ define the terms “gender non-conforming” and “transgender.”

___ identify barriers to health care experienced by transgender individuals

CME Lesson 20: Aggression in Children and Adolescents: Pharmacological Strategies

___ assess clinical guidelines for assessing youth who view NSSI content on the Internet.

___ consider effective treatment strategies to encourage healthy Internet use.

CME Information Page

Overall Objective: 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 April 15, 2018,** 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 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

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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 35 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.

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Accreditation Standards: IOM; ACGME / ABMS Competencies

Directions in Psychiatry, Vol. 38

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 / ABMS Competencies:

Patient Care and Procedural Skills demonstrate compassionate, appropriate, and effective care for the treatment of health problems and promote 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 demonstrates awareness of and responsibility to the larger context and system of health care as well as the ability to call on system resources to provide care that is of optimal value.

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. 38 * 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	X
Employ evidence-base practice	X	X	X	X	
Apply quality improvement	X	X	X		
Utilize informatics					X
ACGME Competencies					
Patient care				X	
Medical knowledge	X	X	X	X	X
Practice-based learning and improvement	X			X	X
Interpersonal and communication skills				X	
Professionalism				X	X
System-based practice		X	X		
ABMS MOC Competencies					
Professional standing				X	X
Commitment to lifelong learning	X	X	X	X	X
Cognitive expertise				X	
Performance in practice				X	

Accreditation Standards: IOM; ACGME / ABMS Competencies

Directions in Psychiatry, Vol. 38

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Directions in Psychiatry, Vol. 38 * Part 2					
IOM Core Competencies	**Lesson 6**	**Lesson 7**	**Lesson 8**	**Lesson 9**	**Lesson 10**
Provide patient-centered care	X	X		X	X
Work in interdisciplinary teams		X		X	
Employ evidence-base practice		X	X	X	
Apply quality improvement		X			
Utilize informatics	X				
ACGME Competencies					
Patient care	X	X	X	X	X
Medical knowledge			X	X	X
Practice-based learning and improvement			X	X	
Interpersonal and communication skills				X	
Professionalism				X	
System-based practice		X	X		
ABMS MOC Competencies					
Professional standing				X	
Commitment to lifelong learning	X	X	X	X	
Cognitive expertise		X		X	
Performance in practice		X			

Accreditation Standards: IOM; ACGME / ABMS Competencies

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Directions in Psychiatry, Vol. 38 * Part 3					
IOM Core Competencies	**Lesson 11**	**Lesson 12**	**Lesson 13**	**Lesson 14**	**Lesson 15**
Provide patient-centered care		X		X	X
Work in interdisciplinary teams					
Employ evidence-base practice	X		X	X	
Apply quality improvement				X	
Utilize informatics					
ACGME Competencies					
Patient care		X		X	X
Medical knowledge		X	X	X	X
Practice-based learning and improvement	X		X	X	
Interpersonal and communication skills		X			
Professionalism					
System-based practice					
ABMS MOC Competencies					
Professional standing					
Commitment to lifelong learning	X	X	X	X	X
Cognitive expertise				X	
Performance in practice					X

Accreditation Standards: IOM; ACGME / ABMS Competencies

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Directions in Psychiatry, Vol. 38 * Part 4					
IOM Core Competencies	**Lesson 16**	**Lesson 17**	**Lesson 18**	**Lesson 19**	**Lesson 20**
Provide patient-centered care	X	X	X	X	X
Work in interdisciplinary teams					
Employ evidence-base practice			X	X	
Apply quality improvement	X	X		X	
Utilize informatics	X	X		X	
ACGME Competencies					
Patient care	X	X	X	X	X
Medical knowledge	X	X	X	X	X
Practice-based learning and improvement				X	
Interpersonal and communication skills				X	
Professionalism	X	X		X	
System-based practice	X	X		X	
ABMS MOC Competencies					
Professional standing	X	X			
Commitment to lifelong learning	X	X	X	X	X
Cognitive expertise	X	X	X	X	
Performance in practice	X	X		X	X

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. The editorial advisory board members consult with staff of The Hatherleigh Company, Ltd. regarding the content of continuing medical education content, but do not directly control the content.

For this publication, relationships, if they exist, between the *Directions in Psychiatry* faculty, program advisors, Hatherleigh staff, their immediate family members, and commercial and pharmaceutical companies in accordance to the Accreditation Council for Continuing Medical Education (ACCME) guidelines are listed 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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The following faculty have no conflicting interests to disclose.

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Dr. Newcorn is a consultant with Enzymotec Ltd., NLS Pharma Group, Pfizer Inc., Rhodes Pharmaceuticals, Shire Pharmaceuticals, and Sunovion Pharmaceuticals, Inc. He is on the advisory board with Akili Interactive, Arbor Pharaceuticals, LLC, Medice, Shire Pharmaceuticals, Supernus Pharmaceuticals. He has received a research grant for Shire Pharmaceuticals, Supernus Pharmaceuticals, and Otsuka Pharmaceuticals.

Advisory Board Member Disclosures:

The following editorial board members have no conflicting interests to disclose.

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Hatherleigh Editorial Staff Disclosures:

The following staff members have no conflicting interests to disclose.

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Directions in Psychiatry

Breakdown of Tested Areas for Volume 38

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	
	4	A	A	**3 out of 4 questions correct for the lesson**

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

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Cannabis: Medicine or Mayhem? Part I: History and Epidemiology

Drew W. Edwards, EdD, MS; Mark S. Gold, MD, DFASAM, DLFAPA

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

KEY WORDS: Cannabis Use Disorder • Marijuana • *Delta-9-tetrahydrocannanbinol* (THC) • *Cannibidiol* (CBD) • Anandamide • Endocannabinoid • Cannabinoid Receptors • Co-Occurring Mental Illness • Surveillance and Prevalence.

LEARNING OBJECTIVES: After completing this educational activity, participants will be able to (1) summarize the history, trends, and prevalence of marijuana use and *marijuana use disorder* (MUD) in the United States; (2) describe epidemiological trends that influence prevalence rates; and (3) delineate attitudes toward legalization of the medicinal and recreational use of marijuana and their impact on prevalence.

LESSON ABSTRACT: Marijuana is the colloquial name for a common intoxicant made from the flowering components of the female *Cannabis sativa* plant. Its psychoactive ingredient Δ^9*-tetrahydrocannabinol* (THC)—is a poorly understood lipophilic cannabinoid that causes dopamine levels in the midbrain to rise. The prevalence of marijuana use in the United States is increasing in nearly all demographic groups. At present, 24 million Americans aged 12 years and older use marijuana, many on a daily basis. Of the 8000 Americans using an intoxicant for the first time on any given day, 7000 will choose marijuana. Unfortunately, the increased prevalence of marijuana use is inversely proportional to the perception of harm. Of particular concern are the deleterious effects of marijuana on the developing brain. Additionally, imaging studies and neurobiological investigations have revealed multiple neuroadaptive and functional deficits associated with marijuana use, even in the brains of early initiates. The life trajectory for young people with these deficits correlates with the highest risk for psychopathological conditions, including psychosis, depression, anxiety disorder, suicidality, cognitive decline, and, most notably, an 8-point loss in IQ by age 38. Other harmful effects include academic failure, unemployment, and multiple failed significant relationships among adults. Persistent use by adults is associated with decreased life expectancy.

COMPETENCY AREAS: This lesson addresses increasingly divisive gaps in information and medical opinions on the safety and efficacy of marijuana. This lesson will help the reader sort out the best available evidence regarding the prevalence and shifting attitudes toward the use of marijuana and provide data physicians can use to develop effective patient education and prevention programs and improve clinical care.

Background

The oldest known written record of cannabis use comes from a Chinese emperor named Shen Nung in 2727 BC. Ancient Greek and Roman literature also reveals their knowledge of cannabis and its psychoactive effects. Its use as a euphoriant and for medicinal purposes quickly spread from the Middle East throughout the Islamic empire to North Africa. In 1545 AD, cannabis was brought to the western hemisphere by Spaniards who imported it to Chile for use as a fiber. In North America, cannabis, in the form of hemp, was grown on many plantations to make rope, clothing, and paper.

Over the past 25 years, the use of marijuana has been a source of much political, legal, medical, and social controversy. Today, it is the most frequently used illicit drug of abuse in the United States. It became popular and widely abused in the United States during the mid to late 1960s and 1970s in lock step with the dramatic social changes and unrest occurring during that era.

Prevalence

Marijuana use is increasing in nearly all demographic groups in the United States (US). At present, 24 million Americans aged 12 years and older use marijuana, many on a daily basis.[1] Among the 8000 Americans using an intoxicant for the first time today (mostly teens and children), 7000 will choose marijuana.[9] Early initiation is associated with an increased risk for addiction and psychopathology.

Best Available Evidence:

- **Overall, the percentage of persons aged 12 years or older who used marijuana in 2016 was nearly twice the percentage reported between 2002 and 2015. At present, an estimated 24 million Americans use marijuana.**
- **Among adolescents (aged 12-17 years), 6.5% used marijuana in 2016; approximately 1.6 million adolescents reported using marijuana during the past month.**
- **Among young adults aged 18 to 25 years, approximately 20% (7.2 million) reported using marijuana in 2016.**
- **Among persons aged 26 and older, more than 7% (15.2 million persons) reported using marijuana in 2016.[10, 11]**
- **The highest percentage of marijuana users and persons with *marijuana use disorder* (MUD) was found among adults aged 18-29 years. In this age group, marijuana use rose from 10.5% to the current rate of 21.2% over the past decade.**
- **The most notable increase in prevalence of marijuana use and MUD marijuana use disorder was among black and Latino individuals.**
- **The increase in marijuana use over the past decade was statistically significant in all demographic groups.**

Marijuana Use Disorder

After alcoholism, MUD is cited most often as the reason for admission to substance abuse treatment programs.[3] It has been well established that attitudes regarding the harm in marijuana use is predictive of prevalence. Estimates of MUD vary considerably, in part because of new terminology and definitions associated with this disorder in the *Diagnostic and Statistical Manual of Psychiatric Disorders—5th Edition* (DSM-5)[12] where it is described as a spectrum disorder that includes misuse, abuse, and addiction.

According to the DSM-5, current criteria for MUD include the following common symptoms:

- **Taking the drug in larger amounts or over a longer period than was intended by the user.**
- **A persistent desire to cut down or control one's use and unsuccessful efforts to do so.**
- **Failure to fulfill major obligations at work, school, or home as a result of marijuana use.**
- **Increased tolerance and/or occurrence of withdrawal symptoms during abstinence.[13]**

Some clinicians report difficulty in determining where the lines separating the various symptoms and sequela for MUD should be drawn. As a result, the percentage of patients meeting the criteria for advanced MUD is not as

clear as we would like it to be. At present, the prevalence of advanced MUD ranges from approximately 9.5% to 30% of all users. This range is higher, however, among those who initiated marijuana use during adolescence. The *National Institute on Drug Abuse* (NIDA), for example, estimates an overall addiction rate of 9.5% for all users aged 12 and older and 17% for those who started using during their teens. The *Substance Abuse and Mental Health Services Administration* (SAMHSA) reports that marijuana is the primary substance of abuse for treatment admissions reported for those who started using it at age 14 years or younger (29.2%). Those who started using marijuana at age 11 years or younger comprised nearly one-third of all treatment admissions (32.6%).[14] These data suggest that the most harmful effects of marijuana are associated with early initiation, when the user's brain is still developing and most vulnerable to social pressures.[15] According to SAMHSA treatment episode date (2011), the treatment admission rate for persons 12 and older, citing marijuana as their primary drug of choice was 14 percent higher in 2011, at 125 per 100,000 population, than in 2001 (110 per 100,000).

Adolescent Marijuana Use

In 1975, NIDA, in partnership with the University of Michigan, initiated the annual *Monitoring the Future* (MTF) survey[3] which serves as the gold standard in epidemiological research on adolescent and, more recently, childhood drug use. Data collected since 1975 indicate numerous changes in the perception and prevalence of drug use among our nation's youngest, most vulnerable citizens. According to the MTF survey, the pinnacle of adolescent drug use, particularly use of marijuana, was reached in 1979. By then, 60.4% of 12th-grade students reported having used marijuana at some time during

Table 1:
Marijuana Use in the Past Year among Persons Aged 12 or Older, by Age Group and Demographic Characteristics: Numbers in Thousands, 2015 and 2016

Demographic Characteristic	Aged 12+ (2015)	Aged 12+ (2016)	Aged 12-17 (2015)	Aged 12-17 (2016)	Aged 18+ (2015)	Aged 18+ (2016)	Aged 18-25 (2015)	Aged 18-25 (2016)	Aged 26+ (2015)	Aged 26+ (2016)
TOTAL	36,043[a]	37,570	3,137	2,982	32,906[a]	34,588	11,246	11,401	21,660[a]	23,187
GENDER										
Male	20,934	21,839	1,636	1,483	19,299	20,357	6,311	6,254	12,988[a]	14,103
Female	15,109	15,731	1,502	1,499	13,607	14,232	4,935	5,148	8,673	9,084
HISPANIC ORIGIN AND RACE										
Not Hispanic or Latino	30,851[a]	32,303	2,412	2,300	28,439[a]	30,003	9,073	9,229	19,366[a]	20,774
White	23,248	24,298	1,736	1,625	21,512	22,673	6,457	6,723	15,056	15,950
Black or African American	5,403	5,341	437	416	4,966	4,925	1,756	1,669	3,210	3,256
American Indian or Alaska Native	260	298	18	24	242	273	84	*	158	178
Native Hawaiian or Other Pacific Islander	106	153	*	*	77	146	*	*	34	91
Asian	835	1,009	56	81	779	929	353	355	425	573
Two or More Races	1,000	1,204	136	148	863	1,057	379	331	484[a]	725
Hispanic or Latino	5,192	5,267	725	683	4,467	4,585	2,173	2,172	2,294	2,413
EDUCATION										
< High School	da	da	da	da	4,161	3,979	1,634	1,472	2,527	2,507
High School Graduate	da	da	da	da	8,627	8,836	3,346	3,383	5,281	5,453
Some College/Associate's Degree	da	da	da	da	12,050[a]	12,978	4,885	5,118	7,164	7,860
College Graduate	da	da	da	da	8,069	8,795	1,380	1,429	6,689	7,367
CURRENT EMPLOYMENT										
Full-Time	da	da	da	da	17,042	18,004	4,847	4,872	12,194	13,132
Part-Time	da	da	da	da	5,770	6,199	3,064	3,292	2,706	2,907
Unemployed	da	da	da	da	2,721	2,885	1,286	1,275	1,435	1,610
Other[1]	da	da	da	da	7,373	7,500	2,048	1,962	5,325	5,538

* = low precision; -- = not available; da = does not apply; nc = not comparable due to methodological changes; nr = not reported due to measurement issues.

[a] The difference between this estimate and the 2016 estimate is statistically significant at the .05 level. Rounding may make the estimates appear identical.
[b] The difference between this estimate and the 2016 estimate is statistically significant at the .01 level. Rounding may make the estimates appear identical.

[1] The Other Employment category includes students, persons keeping house or caring for children full time, retired or disabled persons, or other persons not in the labor force.

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2015 and 2016.

their lives, 50.8% reported using it during the previous 12 months, and 10.3% reported using it on a daily basis. At that time, the MTF survey was limited to high school seniors, in part because of the widely held belief that adolescent drug use was extremely rare and limited to a very small cohort within the "counterculture." It is interesting to note that people who were high school students in the early 1980s are the parents of adolescents and millennials today and that marijuana use is at the highest rate in these two groups among all age cohorts today.

By the mid 1980s, the use of all illicit drugs had begun to decline. The use of cannabis declined steadily from a high of 60% to a low of 32.6% among 12th-grade students in 1992. Specifically, marijuana use during the 12 months preceding the survey fell from 51% to 22%, and daily use fell from 10.3% to less than 1.9%. Overall, this represented the largest decline in adolescent drug use in U.S. history.

The question is: Why?

The answer may lie in the direct correlation between prevalence of psychoactive drug use and perception of harm. Thus, this dramatic decline in marijuana use may have been due largely to the increase in school- and community-based education and prevention programs, many of which were brought forth through parent organizations—such as "Families in Action"—that exerted tremendous pressure on local municipalities and school boards when the burgeoning drug problem spread to middle- and upper middle-class communities. The "Just Say No" program provided funding, educational resources, and structure in local communities that triggered a dramatic shift in parental awareness, as well as parental involvement in civic and school activities. By the end of the 1980s, polls by the Gallup Organization revealed a significant rise in the number of Americans who "personally disapproved" of drug use.

Prevalence data for 2016 revealed the following:

- **24.0 million Americans aged 12 years or older were current users of marijuana.**
- **1.6 million adolescents (6.5%) used marijuana regularly.**
- **7.2 million individuals aged 18 to 25 years (20.8% of the U.S. population) were using marijuana.**[16]
- **Approximately 10% to 30% of persons using marijuana demonstrated evidence of a *substance use disorder* (SUD).**
- **Initiation of marijuana use during early and mid-adolescence is associated with an increased risk for addiction, suicidality, and other co-occurring psychiatric disorders.**

In response to the rising prevalence and potency of marijuana, George Koob, PhD, Director of the *National Institute on Alcohol Abuse and Alcoholism* (NIAAA), stated the following:

> *Based on the results of our surveys, marijuana use in the United States has risen rapidly over the past decade, with about 3 in 10 people who use marijuana meeting the criteria for addiction. Given these increases, it is important that the scientific community convey information to the public about the potential harms.*

Trends and Attitudes Regarding Legalization

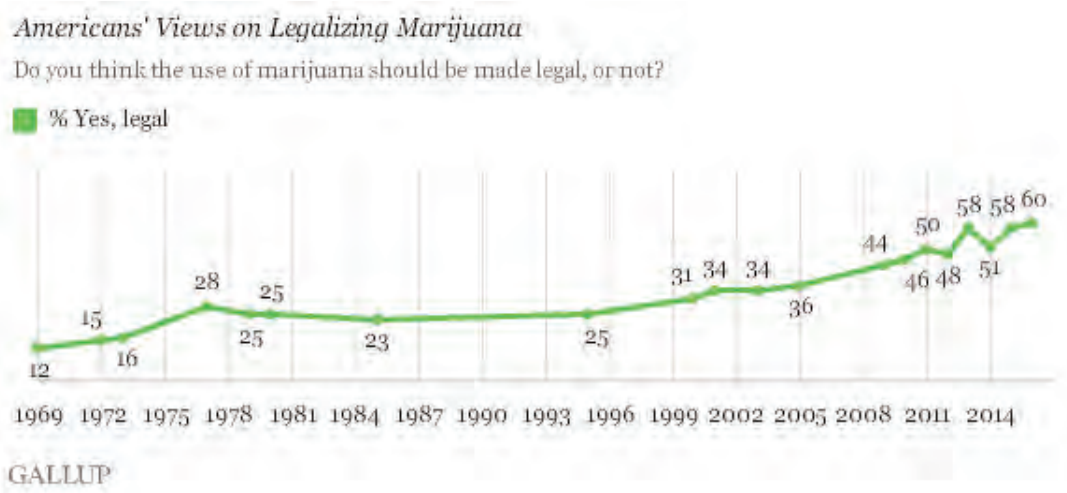
At present, 30 states and the District of Columbia have laws broadly legalizing the use of marijuana in one form or another. Of these, eight states and the District of Columbia have adopted the most expansive laws allowing for its recreational use. The most recent legalization decision was made in California, where marijuana became available for recreational use on January 1, 2018. With the continued liberalization of marijuana laws, the proportion of the population that considers marijuana to be a harmless drug has increased. In states where it is legal to purchase and use marijuana for recreational purposes, the prevalence of use and MUD has increased the most.

Shifting Attitudes:

The Gallup poll first included the question, "Do you think marijuana should be made legal?" in 1969. At that time, 12% of Americans said yes. By the late 1970s, the Gallup survey showed that support for legalization had risen to 28%. It declined slightly during the 1980s, reaching a low of approximately 25% by 1995. It then changed course, increasing to 31% in 2000, and has continued to climb since then, reaching to 60% in 2016.

Table 2:
Gallup Polling National Survey

Gallup Polling National Survey 1969—2016
"Do you think the use of marijuana should be legal?"



Poll results are based on telephone interviews conducted October 5-9, 2016, using a random sample of 1017 adults aged 18 and older living in all 50 United States and the District of Columbia. For results based on the total sample of US adults, the margin of sampling error is ±4% at the 95% confidence level. All reported margins of sampling error include computed design effects for weighting.

The increased prevalence of marijuana use, combined with the increased potency of marijuana today, can lead to neuroadaptation through the degradation of neuronal circuitry in some areas of the brain and loss of neurotransmission among important functional areas of the brain. The presentation of psychiatric symptoms and emergencies—including panic attacks, severe anxiety, depression, suicidality, psychosis, and drug-induced schizophrenia—has increased with the increased use of the highly potent marijuana that is currently available.[17]

Risk and Protective Factors:

Adverse childhood experiences (ACE) are associated with SUDs. Approximately half of all children in the United States have experienced an ACE, such as the following:

- **physical abuse (28.3%)**
- **substance misuse in the household (26.9%)**
- **sexual abuse (girls: 24.7%; boys: 16%)**
- **parent's divorce or separation (23.3%)**
- **Lack of mutual attachment and nurturing by parents or caregivers**

Other risk factors for SUD include:

- **ineffective parenting**
- **a chaotic home environment**
- **lack of a significant relationship with a caring adult**
- **a parent or caregiver with an SUD or mental illness or who engages in criminal behavior**
- **behavioral problems in school, such as aggression and impulsivity**
- **academic failure**
- **poor social coping skills**
- **association with peers with problematic behaviors, including drug use**
- **Misperception of the extent and acceptability of drug-abusing behaviors**

Protective factors include the following:

- **a strong bond between the child and his/her parents or caregivers**
- **parents who are highly involved in their child's life**
- **parents who do not abuse psychoactive substances**
- **supportive parenting ensuring that the financial, emotional, academic, and social needs of the child are met**
- **clear limits and expectations established for behavior**
- **age-appropriate monitoring of social behavior (e.g., curfews) and social media, adult supervision, constant awareness of the whereabouts of the child, knowing the child's friends, and enforcement of household rules**
- **success in academics and involvement in extracurricular activities**
- **strong bonds with positive social institutions, such as schools or religious organizations**
- **acceptance of norms against drug misuse**

Summary

The data presented in this lesson highlight the dynamic prevalence of marijuana use and incidence of MUD, as well as changing attitudes toward use, perception of harm related to marijuana use, and risk and protective factors associated with both the initiation of use and addiction. Given the current prevalence and trends in early initiation of use, resources are overloaded. This has created additional public health and safety challenges, such as driving under the influence, unemployment, academic failure, increased crime, and limited access to effective treatment. Therefore, the capacity for parents and caregivers to provide a safe, nurturing, and protective environment while addressing and limiting known risk factors associated with SUDs is perhaps the most viable protective factor.

About the Faculty

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Multiple-Choice Questions

1. According to this lesson which of the following is *not* one of the criteria for marijuana use disorder?

A. Previous or concurrent psychiatric disorder

B. Failure to fulfill major obligations at work, school, or home as a result of marijuana use

C. Taking the drug in larger amounts or over a longer period than was intended by the user

D. Inability to cut down or control use

2. According the Annual Monitoring the Future study, in which year was the prevalence of drug use among high school seniors the highest?

A. 2013

B. 1979

C. 1992

D. 1984

3. All of the following are protective factors associated with the development of marijuana use disorder, *except:*

A. Strong bonds with pro-social institutions, such as schools or religious organizations.

B. Parents teaching their children to smoke marijuana appropriately.

C. Involvement in extracurricular activities.

D. Having parents or caregivers who strictly enforce household rules and curfew.

4. Regarding the prevalence of marijuana use in the United States, which of the following statements is *not* true?

A. Early initiation correlates highly with the development of marijuana use disorder.

B. Marijuana use among high school students was highest in the 1990s.

C. Parental involvement in the community and schools helps reduce adolescent drug use.

D. The belief that marijuana is harmless is associated with increased prevalence.

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Best Practices in CME

Cannabis: Medicine or Mayhem?
Part I: History and Epidemiology

Drew W. Edwards, EdD MS; Mark S. Gold, MD, DFASAM, DLFAPA

ID#: L003404

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 is designed to help clinicians understand the history, prevalence, and epidemiology of marijuana, its use, and associated risk and protective factors.

Key Point 1: Identification

Marijuana use is increasing in nearly every age cohort in the United States. Epidemiological studies have shown an inverse relationship between perception of harm and prevalence of use. Approximately 24 million persons currently use marijuana. Estimates of the number of users meeting the criteria for *marijuana use disorder* (MUD) range from 9.5% to 30%. Those who initiate marijuana use at the youngest age are at the greatest risk for addiction.

The best available evidence suggests that marijuana elevates dopamine levels in the midbrain and disrupts neuronal circuitry between the midbrain and *prefrontal cortex* (PFC), causing deficits in the inhibitory function of the PFC that result in the loss of behavioral control. Early initiation of use and persistent use are associated with increased morbidity, including risk of addiction, depression, anxiety disorder, psychosis, schizophrenia, suicidality, academic failure and underachievement, unemployment, and multiple failed significant relationships.

Key Point 2: Triage

Clinicians in various settings should screen patients regularly for signs of substance use disorder; in the case of marijuana use, they should also screen for signs of co-occurring psychiatric disease, including abuse or addiction to other intoxicants. The current criteria for MUD include:

- **Taking the drug in larger amounts or over a longer period than was intended by the user.**
- **Persistent desire to cut down or control one's use of marijuana and unsuccessful efforts to do so.**
- **Failure to fulfill major obligations at work, school, or home as a result of marijuana use.**
- **Increased tolerance and/or evidence of protracted withdrawal symptoms during abstinence.**

Clinicians should be prepared to discuss, identify, assess, or refer patients with a suspected MUD to an addiction medicine specialist or addiction psychiatrist.

Key Point 3: Treatment

Given the high rate of psychiatric disease co-occurring with MUD, clinicians who provide treatment for SUDs should provide multimodal psychosocial treatment options and/or be knowledgeable of these resources in their community.

Key Point 4: Medications

Clinicians treating patients for marijuana dependence should understand that cannabis is a lipophilic substance and, thus, can remain in the brain and adipose tissue for weeks. Therefore, withdrawal can be protracted and symptoms may emerge slowly, sometimes weeks after discontinuation. Symptoms include depression, agitation, anxiety, sleep problems, boredom, lethargy, and difficulty focusing.

If these psychiatric symptoms occur and persist at a clinical level, clinicians should be prepared to treat or refer, as part of a patient-centered approach.

No medication is indicated for the treatment of MUD. Given the rate of concordance between SUD and depression, the prevalence of anxiety disorder is between 45% and 65%. Accordingly, the use of medication and/or other therapies (e.g., mindfulness meditation) for a co-occurring psychiatric illness or psychiatric symptoms during withdrawal is acceptable unless contraindicated.

Key Point 5: Informed Consent

When the use of medication is indicated, the clinician should educate the patient regarding the risks and benefits of the drug and re-assess the patient's level of motivation for treatment regularly. Each medication has unique qualities and side effects that may require additional monitoring and reassessment during treatment.

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Opioid Use Disorder: A Review of Medication-Assisted Treatment and Psychosocial Programs

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LEARNING OBJECTIVES: Upon reading this lesson, readers will (1) recognize the prevalence and epidemic of *opioid use disorder* (OUD) and its increasingly deadly nature. Readers will identify approved medications for opioid use disorder to administer effective treatment. Lastly, readers will differentiate primary psychosocial programs for treating OUD enabling them to be comfortable discussing these with patients.

LESSON ABSTRACT: The rate of *opioid use disorder* (OUD) is increasing rapidly and with increasingly deadly outcomes. It has been declared an epidemic in the United States. *Medication-assisted therapy* (MAT) is critical for patients with OUD to achieve short- or long-term sobriety. Methadone, buprenorphine, and naltrexone are approved for maintenance therapy in OUD. Although these medications differ in terms of mechanism of action, application, and route of administration, they are all effective in reducing illicit opioid use and, in turn, decreasing the frequency and severity of many psychosocial and medical complications associated with this disorder. The selection of effective medications is limited, but these should be considered for all patients with OUD. Patients should also be told about any psychosocial support programs that are available to them. The combination of MAT and psychosocial support is the most effective method of managing OUD.

Introduction

Opioids—including *oxycodone* (Oxycontin), *hydrocodone* (Norco, Vicodin) and *morphine* (Duramorph, Infumorph P/F)—are prescribed for acute and chronic pain control. They achieve this by activating specific G-protein-coupled receptors (mu, kappa, delta), which begins the process of signal transduction. This leads to analgesic and central nervous system depressant effects and the potential to cause euphoria. Physiologic dependence involves the need for more opioids to achieve the same effect, and withdrawal symptoms occur upon cessation. *Opioid use disorder* (OUD) is characterized by cravings, loss of control and compulsive use despite the negative consequences. Physiologic dependence is often present with an OUD but is not a necessary component. Many individuals who develop an OUD will transition from prescriptions to heroin and from swallowing pills, to insufflation and IV use. OUD is a chronic, relapsing illness with increased rates of morbidity and mortality.

The incidence of OUD has been and continues to be growing very rapidly in the United States. The number of deaths due to an opioid overdose quadrupled between 1999 and 2015.[1] Between 2015 and 2016, they increased dramatically, with the majority of the increase accounted for by a surge in deaths related to the use of *fentanyl* (Duragesic, Subsys, Abstral) and fentanyl analogs.[3] Deaths from a drug overdose climbed to more 500,000 during this time period (2000-2015); currently, 91 Americans die from an overdose every day. Drug overdose is now the leading cause of accidental death in the United States, with opioids implicated in more than half of these deaths.[2] Most of these drug overdose-related deaths were accidental, although some were the result of poisoning or suicide.

OUD also has serious health consequences. Patients often appear debilitated and in poor general health. The use of contaminated drugs and inadequate sterilization of drug paraphernalia puts them at increased risk for localized and systemic infections, including cellulitis, abscesses, endocarditis, and osteomyelitis, as well as infection from such blood-borne pathogens such as the *human immunodeficiency virus* (HIV) and hepatitis B or C virus (HBV or HCV). Patients with OUD also have also demonstrated increased rates of opioid-induced bowel syndrome and hyperalgesia, as well as accidents. They are also likely to demonstrate high rates of psychosocial disorders that result in incarceration and failed relationships. A 30-year follow-up study of opioid-dependent young adults showed a very high rate of relapse into drug dependency and a mortality of nearly 50%.[4]

Because of the rapidly growing incidence and mortality associated with OUD, it has been declared an epidemic in the United States. As a result, increased attention is currently being paid to its treatment and prevention. **It is now widely accepted that *medication-assisted treatment* (MAT) is a critical part of the ongoing management of this disorder. MAT is the use of medications in combination with counseling and behavioral therapy in a whole-patient approach to treatment. The counseling and behavioral therapies include twelve-step programs, *community reinforcement and family training* (CRAFT), *cognitive behavioral therapy* (CBT), the *Self-Management and Recovery Training* (SMART Recovery) program, individual and group counseling, case or care management, recovery support services, and peer support.** The primary focus of this lesson will be on MAT for OUD involving the use of *methadone* (Methadose, Diskets), *buprenorphine* (Suboxone, Zubsolv), or *naltrexone/extended-release naltrexone* (NTX/XR-NTX). A brief review of major psychosocial support programs is also provided.

Methadone

Methadone is a synthetic opioid that acts as a full mu receptor agonist. Developed more than 70 years ago, methadone currently has *US Food and Drug Administration* (FDA) approval for the treatment of individuals with chronic pain and for maintenance therapy in patients with opioid dependence. Many reviews confirm that methadone maintenance plays a vital role in reducing morbidity and mortality among opioid-dependent patients.[5-8] Its use in individuals with OUD is subject to a considerable number of regulations, however, and it must be administered as part of a structured program. Its efficacy is improved when the patients participate in psychosocial treatment programs while receiving the drug[9] and are monitored very closely[10] during the early phases of treatment. Patients are required to go to a clinic to receive methadone, which is generally administered in liquid form in a 10-mg/mL dose, although other doses are available. At the clinic, they are allowed to take at least one

dose home. Over time, the number of "take-home" doses increases and the number of clinic visits decreases. During the first 3 months, for example, patients are required to go to the clinic 6 days per week and take methadone in the presence of a staff member; the patient is given a single take-home dose, typically to be taken on a Sunday. During the next 3 months, the patient receives two take-home doses, generally for use on Saturday and Sunday. During the following 3 months, the patient receives four take-home doses and goes to the clinic 3 days a week, usually on a Monday, Wednesday, and Friday. After one year of treatment, the patient goes to the clinic one day per week and receives six take-home doses. Throughout their treatment, these patients undergo a supervised urine drug screening and breathalyzer test at each visit.

Methadone has a high street value, and rates of diversion to street sales and other illicit uses can be quite high. Attempts at diversion prevention include the requirement to go to a clinic for most of the doses initially and the addition of a small amount of dye to the take-home dose (which is normally a clear solution) to discourage patients from administering take-home doses intravenously for a stronger effect.

The patient is also monitored closely for the efficacy of the drug. Extensive studies have shown that the efficacy of higher doses of methadone tend to be superior to that of lower doses.[11] Dose adjustments and maximums are generally determined at the discretion of the clinic. Patients usually initially receive a low dose (20-30 mg) and are monitored closely for tolerability. The dose may be raised 5 mg daily until it reaches approximately 80 mg; thereafter, it is usually raised at a slower rate. **The standard effective dose is considered to be in the range of 80 to 120 mg, although some patients may require an even higher dose.** The effective methadone dose can vary significantly among patients because of differences in their metabolic rates and interactions between methadone and other medications.

Many factors are considered to determine the duration of treatment, including the substance the patient is dependent on (heroin being considered more severe), the number of prior relapses, the success of previous methadone treatments, the duration of current sobriety, and the structure of the ongoing treatment program. If the patient is to be tapered off methadone, the process must take place in a carefully monitored and controlled environment over several months, during which time the dose is gradually reduced. During this period of time, the patient is at risk of a relapse and the induction of withdrawal symptoms; therefore, this method should only be attempted after careful consideration. Patients are often switched from buprenorphine to methadone without complications in a manner similar to that used to stop the use of any other opioid. **Switching from methadone to buprenorphine, however, requires careful reduction of the methadone dose followed by close monitoring of the patient for symptoms of buprenorphine-induced withdrawal syndrome.**

Opioid dependence often has the unfortunate consequence of death from an overdose; infection with HIV, HBV, or HCV; and criminal activity. Thus, the intended outcome of treatment is not only discontinuation of the illicit use of opioids, but also harm reduction, i.e., reduction in the psychosocial and medical consequences of opioid dependence and protection against an overdose. Methadone continues to have the best rates of medication adherence, even over years. Unfortunately, the stigma associated with this drug may discourage providers from referring patients to maintenance treatment programs or discourage patients from accepting referrals to such programs.

The potential for methadone abuse is high and often occurs synergistically through the use of other opioid medications. The risk of respiratory depression is particularly high when methadone is used in conjunction with alcohol and/or benzodiazepines. The peak respiratory depressant effect occurs after the peak analgesic effect has set in and is often underestimated. Therefore, methadone should not be administered to a patient who is currently intoxicated and should be used with extreme caution in patients who are not known to be abstaining from alcohol or benzodiazepines. Methadone should also be administered with caution to any patient with a respiratory disorder.

Methadone should also be administered with caution to patients with abnormal *cardiovascular* (CV) findings. It has the potential to induce QTc prolongation and serious arrhythmias; therefore, an *electrocardiogram* (ECG) should be administered at baseline and routinely throughout the treatment period. It may also cause hypotension

(including orthostatic hypotension), as well as dizziness, sedation, *gastrointestinal* (GI) distress, sweating, and other adverse CV effects.[12]

Drug-drug interactions are an additional concern during methadone maintenance therapy. Methadone is metabolized via the cytochrome P450 system. Therefore, any other medication that induces or inhibits cytochrome P450 enzymes will be of clinical relevance.

Buprenorphine

Buprenorphine is a Schedule 3 synthetic opioid that functions as a partial agonist at the mu opioid receptor and is used both in the detoxification and maintenance of opioid-dependent patients. Following the *Drug Addiction Treatment Act* (DATA) of 2000, buprenorphine was approved by the FDA for opioid maintenance therapy in office settings. While still subject to restrictions, its use in office settings provides clinicians and patients considerably more flexibility compared with methadone. Buprenorphine is available in three primary formulations for opioid dependence: (1) buprenorphine monotherapy; (2) buprenorphine/naloxone combination therapy; and (3) implantable buprenorphine. In combination therapy, naloxone has no oral bioavailability and serves as a means of reducing the need for non-oral forms of the drug, as well as for preventing diversion. As a partial agonist at the mu opioid receptor, buprenorphine exerts weaker effects than a full mu opioid agonist (e.g., methadone), which makes it safer to use in patients experiencing an overdose. Its relatively long duration of action makes withdrawal from buprenorphine easier to achieve than withdrawal from methadone and makes it more acceptable for alternate-day dosing. In addition to its role in opioid maintenance, buprenorphine has an indication for pain control.

A recent meta-analysis[13] of 25 studies involving 4497 participants with OUD was carried out to investigate the efficacy of buprenorphine versus methadone and placebo for opioid maintenance. Primary outcome measures included retention in treatment, relapse to opioid use, use of other substances, criminal activity, and mortality. Both fixed-dose (use of a dose within a very narrow range with no adjustment following stabilization) and flexible-dose (titration of the dose according to participant preference) methods were used. Buprenorphine was found to be superior to placebo in terms of program retention and suppression of heroin use at medium and high doses but less effective than methadone in achieving retention and in suppressing heroin use. The authors concluded that buprenorphine should be used for maintenance therapy when high doses of methadone cannot be administered or methadone is not tolerated. They do note, however, that the unique pharmacologic properties of buprenorphine and the limited number of restrictions surrounding its use, along with the possibility of alternate-day dosing, may make it a preferred choice over methadone in many patients.[13]

Oral buprenorphine is usually taken daily, which may lead to problems with patient compliance. Because an implant can reduce barriers such as noncompliance, forgetfulness, diversion, and deliberate overdosing, long-acting implants are becoming a preferred route of administration. Long-acting formulations may be particularly beneficial when access to care is limited. Implants can remain effective to 6 months;[14-16] providing a regulated, constant dose, they can be used to achieve stable blood levels of the drug. In 2010, the efficacy of buprenorphine implants was investigated in a 6-month randomized, placebo-controlled trial carried out in 18 US sites in 163 adults with OUD. When urine samples were tested for illicit opioids, the investigators collected a greater percentage of negative samples from patients with a buprenorphine implant compared with those with a placebo implant. They also found fewer buprenorphine patients reporting withdrawal symptoms compared with those who received the placebo. Furthermore, a higher rate of global improvement was determined for buprenorphine recipients with only minor adverse reactions.[17] In another 6-month study, Rosenthal et al[18] compared the combination of a buprenorphine implant with a placebo tablet versus a placebo implant with a buprenorphine tablet in 177 patients who had previously been stable for 90 days or longer on <8-mg doses of sublingual buprenorphine/naloxone. More patients in the buprenorphine implant arm remained abstinent from illicit opioids for at least 4 months compared with those who had received sublingual formulation, although a greater number of implant recipients experienced mild adverse events.

According to *DATA 2000,* physicians must meet certain requirements and notify the Secretary of the *Department of Health and Human Services* (DHHS)

of their intent to prescribe buprenorphine for opioid dependence before doing so. On completing these requirements, physicians will receive a special designation on their *Drug Enforcement Administration* (DEA) license (X-license). During the first year following the date of notification of this designation, physicians may treat up to 30 patients; during the second year, they may treat up to 100 patients. After prescribing buprenorphine for 100 patients over a year or longer, a physician may apply to the DHHS for permission to increase the prescription limit to 275. Patients are typically provided a one-week supply of medications for a designated period of time and then a 2-week supply. After demonstrating sobriety, patients can receive monthly supplies of the drug. By contrast, methadone doses follow a considerably more restrictive schedule, with its least restrictive program (weekly take-home doses) resembling the most restrictive program for buprenorphine. The typical target dose of buprenorphine is 16 mg daily. The typical dose for the implantable formulation was provided in four 80-mg implants.

Buprenorphine should be used as part of a treatment program that includes psychosocial therapy. Patients taking buprenorphine should be closely monitored, especially during the early stages of treatment. There is a significant risk of buprenorphine abuse and diversion; therefore, patients receiving this drug should be checked routinely to make sure they are taking it as prescribed. When taken in combination with other *central nervous system* (CNS) depressants, including benzodiazepines and alcohol, buprenorphine may induce respiratory depression and even death; patients should be adequately warned about this risk. Treatment with buprenorphine can induce symptoms of a withdrawal syndrome. The physician should determine that the patient is already free of other opioids or at least demonstrating symptoms of opioid withdrawal before prescribing buprenorphine to avoid precipitating a withdrawal syndrome and reducing the likelihood that the patient will continue treatment. Buprenorphine has been shown to cause liver impairment; therefore, routine liver function tests should be ordered. The most common routine side effects of buprenorphine are headache, pain, GI distress (including constipation and nausea), insomnia, and sweating. Many of these side effects are less pronounced with buprenorphine compared with heroin or any other opioid of abuse.[19]

The buprenorphine implant is a nonbiodegradable device consisting of four one-inch rods that are inserted subdermally into the upper arm.[15] Common adverse side effects include headache, depression, constipation, nausea, vomiting, back pain, mouth pain, and injection site irritation. Rarely, serious complications may occur during the insertion or removal of the implant.

Buprenorphine is effective for maintenance therapy in patients experiencing opioid dependence and has a safer profile and fewer restrictions than methadone. Head-to-head comparisons often favor methadone in terms of efficacy; however, buprenorphine should be considered in any patient who is unable to tolerate methadone, unable to comply with the restrictive schedule of methadone maintenance, or who may benefit from an alternate-day dosing schedule. Because of the risk for abuse and diversion, patients receiving buprenorphine to overcome substance abuse should always be monitored closely, especially during the early stages of the treatment process. Buprenorphine should always be used in conjunction with psychosocial treatments.

Naltrexone/Extended Release Naltrexone

Naltrexone **(NTX) is an orally available, relatively selective mu opioid receptor antagonist with an indication for OUD.** NTX is non-addicting, produces no euphoria, and provides complete 24- to 72-hour blockade of all opiate effects.[20] An injectable, extended-release formulation of this drug (XR-NTX) was developed to address the problem of medication adherence. In this formulation, the drug molecule is embedded within a polymeric matrix of microspheres of biodegradable polymers[21] that allow the drug to be released over a predetermined period of time ranging from days to months. It allows the maintenance of stable, pharmacologically relevant plasma levels of NTX for at least 28 days[22] while avoiding first-pass metabolism. As a result, a monthly dose that is approximately one-fourth of the oral formulation (380 mg/mo vs an oral dose of 50 mg/d, or 1500 mg/mo) produces a monthly plasma accumulation roughly four times greater than that achieved with the oral dose. Finally, there may be some benefit to the continuous release of XR-NTX over the pulsatile daily dosing of the oral formulation.[23]

XR-NTX was compared to usual treatment (brief counseling and referral to community treatment programs) in 153 participants in an open-label, randomized trial carried out in five centers over 24 weeks.[24] Participants assigned to XR-NTX demonstrated a longer median time to relapse, a lower rate of relapse, and a higher rate of opioid-negative urine samples. No significant differences in major outcome variables were identified at the 78-week mark (approximately 1 year after the end of the study), except for a lack of overdose deaths in the XR-NTX group compared with seven in the usual treatment group. A retrospective analysis of patients in three residential and treatment facilities revealed that the residents who received XR-NTX were less likely to leave against medical advice and more likely to initiate follow-up care.[25] Relapse-free survival—with relapse defined as four consecutive weeks of any non-study opioid detected in the urine or self-report or seven consecutive days of self-reported use—was evaluated recently in a 24-week, open-label, randomized trial of XR-NTX versus buprenorphine/naloxone in 570 participants in eight US outpatient sites. The investigators found that it was more difficult to interest patients in initiating XR-NTX therapy; this negatively affected their ability to determine overall relapse rates. Once initiated, however, XR-NTX was found to be equal in safety and effectiveness to buprenorphine/naloxone. Although this was not a long-term study, these early results are promising for XR-NTX to be considered an important treatment for OUD.[26]

Duration of Medication-Assisted Therapy

Many factors should be considered when determining the duration of MAT. When a patient has remained sober for an extended period of time, the physician may want to consider discontinuation; if things are going well and the medication is helping, however, the physician may want the patient to continue the medication. Perhaps the first consideration, however, should be the severity of the disorder: The more severe the dependency, the more likely it is that the patient should continue MAT. Tolerability, side effects, drug-drug interactions, cost, and factors affecting on quality of life (e.g., frequency of clinic appointments) must also be taken into consideration. MAT discontinuation should be considered only after the patient has established a solid foundation in a psychosocial program. Ultimately, however, the decision to stop MAT must be based on individual circumstances and made with careful consideration of all risks and benefits.

Psychosocial Programs and Treatment

Psychosocial support programs are integral to a successful outcome with OUD treatment. The following section provides a brief overview of the primary programs currently available.

Alcoholics/Narcotics Anonymous:

Alcoholics Anonymous (AA) is a self-supporting and influential organization[27] with millions of members in countless countries. AA services are provided free of charge, and meetings are readily accessible. Sponsors are available to help during a crisis and help the patient through the steps that are needed to transition from use to recovery. *The Big Book of AA* remains one of the highest selling nonfiction books of all time, with tens of millions of copies sold[28] and millions of people having been helped through this program. In the United States, AA is the source of help that is most commonly sought by people with alcohol-related problems,[29] with more than 55,000 groups holding meetings at least once per week[30] and 5 million people attending groups annually. A recent review[30] indicates that AA helps individuals recover through common process mechanisms associated with enhancing self-efficacy, coping skills, and motivation and by facilitating adaptive social network changes. The authors note that AA effectiveness may lie in its ability to provide free, long-term access and exposure to recovery-related therapeutic elements that patients can dose-adjust according to their need.[30] Clear benefits of AA lie in the fact that it does not cost the healthcare system any money, it is virtually always available to patients, and individuals can remain anonymous during their participation. Many meetings are now available "virtually," which may be appropriate for patients who struggle with anxiety disorders and prefer to participate from home.

Narcotics Anonymous (NA), is a spin-off of the AA program in the 1940s and 1950s. NA uses the traditional 12-step model but applies it to people with varying

substance use disorders. The philosophies and teachings are similar to AA with language variations to apply to non-alcohol addictions. As with AA, NA is free, widely available and may be life-saving. Some NA groups discourage the use of agonist medication-assisted treatments (e.g., *methadone* [Methadose, Diskets, Dolophine] and *buprenorphine* [Buprenex, Butrans, Probuphine]). Given the importance of these medications for many patients, providers must discuss this issue with their patients.

Community Reinforcement and Family Training (CRAFT)

CRAFT works unilaterally with *concerned significant others* (CSOs) to help them engage unmotivated individuals with substance abuse disorders. CSOs are taught skills they can use to modify a loved one's drug-using behavior and enhance their engagement in treatment. Engaged drug users then receive treatment using a *community reinforcement approach* (CRA).[31] CRAFT is designed specifically to engage resistant substance users in treatment and to reduce the physical and psychological distress of the CSO. Studies have suggested that CRAFT is an effective treatment strategy for individuals with alcohol and drug-use disorders. A meta-analysis[32] comparing CRAFT with AA/NA and the Johnson Institute Intervention (a therapeutic technique in which members of the persons social network confront him or her about the damage that drinking or drug use has caused and the action they will take if treatment is refused) revealed that individuals with a substance abuse disorder were three times more likely to seek treatment through CRAFT than through AA/NA ($P < 0.0001$) and twice as likely than through the Johnson Institute Intervention ($P = 0.004$). Overall, CRAFT encouraged approximately two-thirds of treatment-resistant patients to obtain treatment.[33] CSOs showed marked psychosocial and physical improvements in all three modalities (CRAFT, AA/NA and Johnson Institute Intervention). Hence, CRAFT was the only intervention to improve both the engagement of the substance user in treatment and the well-being of the CSO. The majority of available data on CRAFT are for either alcohol or combined substance use disorders; thus, data supporting CRAFT specifically for OUD are limited. Regardless, CRAFT should be considered as a viable psychosocial support option for these patients.

Cognitive Behavioral Therapy (CBT):

CBT is a time-sensitive, structured, present-oriented form of psychotherapy that is directed toward solving current problems and teaching clients skills to modify dysfunctional thinking and behavior. Cognitive-behavioral strategies are based on the theory that learning processes play a crucial role in the development of maladaptive behavioral patterns, such as substance use disorders. Through CBT, individuals learn how to identify problematic behaviors and correct them using a range of skills designed to help individuals stop substance use and address problems that go with it. CBT is effective for a variety of disorders, including substance use disorders. Several meta-analytic studies have provided limited evidence that CBT is effective in reducing substance use. For example, Magill and Ray,[34] in their study of CBT efficacy in adults diagnosed with alcohol or drug/alcohol use disorders, found a small pooled effect, and Irvin[35] found a small overall effect of relapse prevention intervention in alcohol and substance use disorders, as well as smoking.

SMART Recovery:

SMART Recovery is an international nonprofit organization that organizes free face-to-face and online mutual aid groups for individuals with substance or behavioral addictions. The SMART program is self-empowering and evidence-based. In contrast to the AA model of powerlessness and spiritual fellowships, the SMART Recovery program attempts to increase the participant's ability to maintain motivation, identify and cope with cravings, identify and modify irrational thinking and beliefs, and live with greater balance and attention to long-term goals. **The slogan of SMART Recovery is "Discover the power of choice."[36]** This organization promotes therapeutic strategies based primarily on evidence-based CBT techniques and secondarily on motivational enhancement techniques. Atkins and Hawdon[37] found a positive relationship between participation in mutual self-help groups and the duration of continuous abstinence. This relationship did not differ according to the type of self-help group, which suggests that the SMART Recovery program may be as helpful as any other program. Brooks and Penn[38] found some benefit to SMART Recovery techniques in employment status and medical concerns. In a qualitative study, MacGregor and Herring[39] found that

SMART Recovery participants indicated that its groups were very helpful and that they intended to continue in the program over the next 3 months. Although the overall data are limited, they suggest that the SMART Recovery program provides some benefits with minimal risks.

Contingency Management:

Contingency management (CM) interventions are based on the concept that drug use is a form of operant conditioning in which behavior is controlled or shaped by consequences. Hence, the likelihood of substance use is influenced by the context in which it occurs. CM protocols arrange for the regular monitoring of a person's drug use and delivery of an incentive only after drug abstinence has been verified (i.e., through drug-free urine samples).[40] A positive incentive is expected to compete with the reinforcing effects of the drug and increase the likelihood that abstinence will be initiated and maintained.[41] CM is generally a voucher-based reinforcement therapy and prize-based CM procedure. In voucher based reinforcement therapy, the individual is rewarded with a voucher (which can be exchanged for goods and services) each time a desired behavior is performed. In prize-based CM, the individual is allowed to draw from a prize bowl every time a target behavior is exhibited. The draws range from no reward to a large reward. Both of these procedures have been shown to be effective in clinical trials based on extensive empirical evidence. Systematic reviews[42-44] and meta-analyses[45-49] have consistently supported the use of CM. It should be considered an evidence-based therapeutic approach for use in conjunction with MAT.

Summary

OUD is a chronic, extremely common, rapidly growing, very costly, and often deadly disease with many psychosocial and medical consequences. Treatment success is strongly associated with the duration of treatment, and engagement in a treatment program is critical. Outcomes at 5 years have not been generally studied, but excellent outcomes have been reported and confirmed by the return-to-work rate and negative urine tests in impaired health professionals. Options for OUD treatment are not as numerous as for other chronic diseases, but several effective medications are currently available, including methadone, buprenorphine, and XR-NTX. These medications should be considered part of an overall recovery program and presented to patients as options for their recovery.

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Multiple-Choice Questions

5. What is the mechanism of action of buprenorphine?

A. Partial agonist at the mu opioid receptor

B. Full agonist at the mu opioid receptor

C. Antagonist at the mu opioid receptor

D. It depends on the formulation

6. Which of the following dose ranges is generally considered the most effective for methadone in opioid use disorder?

A. 0 mg – 20 mg

B. 30 mg – 50 mg

C. 60 mg – 80 mg

D. > 80 mg

7. Which of the following statements is true about extended-release naltrexone?

A. It is a mu opioid receptor antagonist.

B. It is a small rod implanted into the arm once every 6 months.

C. It is commonly combined with buprenorphine.

D. All of the above are true.

8. Which of the following should be considered in medication-assisted treatment?

A. AA/NA

B. SMART Recovery

C. Contingency Management

D. All of the above

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Best Practices in CME

Opioid Use Disorder: A Review of Medication-Assisted Treatment and Psychosocial Programs

Brian S. Fuehrlein, MD, PhD; Mark S. Gold, MD, DFASAM, DLFAPA

ID#: L003405

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Opioid use disorder (OUD) is a rapidly growing and increasing deadly illness. It has been declared a public health crisis. It is therefore critical that providers understand basic information about the primary treatment approaches. *Medication-assisted treatment* (MAT) is widely considered as an effective and essential part of a recovery program for most patients. Methadone, buprenorphine and extended-release naltrexone are the primary MAT options for OUD. In addition to MAT, psychosocial programs are often critical. These include AA/NA, SMART recovery, CRAFT, CBT and contingency management.

Key Point 1: Background

OUD is an increasingly deadly public health problem and is now the number one cause of accidental death in the US.

Key Point 2: Medication-Assisted Treatment

MAT is a critical component of a recovery program. Methadone is a full agonist at the mu opioid receptor, buprenorphine is a partial agonist at the mu opioid receptor and extended-release naltrexone is an antagonist at the mu opioid receptor. Each of these medications has been proven effective for treating OUD.

Key Point 3: Psychosocial Treatment Programs

A comprehensive approach to recovery will include both MAT and a psychosocial approach. The primary interventions are AA/NA, SMART recovery, CRAFT, CBT for addiction and contingency management. Each of these may play an important role in the recovery of your patients.

Notes

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Food Addiction

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

KEY WORDS: Food addiction • Obesity • Substance use disorders • Eating disorders • Public health

LEARNING OBJECTIVES: Upon completion of this lesson, clinicians will be able to (1) identify the neuroscientific and phenomenological components of food addiction as it relates to substance use disorders and eating disorders; (2) examine treatment strategies for patients with food addiction to select the appropriate one; and (3) describe public health policies that can address food addiction as it relates to obesity.

LESSON ABSTRACT: Food addiction may, in part, explain the pathophysiological process of obesity in some patients and contribute to the current epidemic of obesity. Thus, it may be of prime clinical utility in evaluating and managing the obese patient. We provide herein a comprehensive overview of preclinical and clinical evidence of food addiction, comparing it with substance use disorders and eating disorders and describing treatment strategies. A deeper understanding of this addiction may have public health indications for both research and policy development.

COMPETENCY AREAS: Food addiction should be considered in the evaluation and management of the obese patient. After reviewing this lesson, clinicians will have increased knowledge to (1) explain nosological, epidemiological, phenomenological, neuroscientific, and treatment issues surrounding food addiction; and (2) craft a conceptual framework they can use to assess obese patients.

Introduction

In light of the current obesity epidemic, research into the causality and treatment of obesity has shifted from peripheral causes (e.g., insulin sensitivity and lipid dysregulation) to central causes (e.g., changes in the brain's reward systems that are associated with obesity).[1, 2] Within the latter framework, the concept of "food addiction" has emerged as a possible mechanism through which some individuals become obese. Food addiction shares characteristics of both eating disorders and substance use disorders, making it a useful construct for studying the neuroscience of obesity. Food addiction is phenomenologically similar to *binge eating disorder* (BED) but differs from it in several important ways. First, patients with BED exhibit negative self-valuation, whereas the addictive property of the food itself, combined with state vulnerabilities, produces a phenotype associated with food addiction.[3] In this lesson, the neurobiological and clinical features of food addiction will be explored and a framework for the clinical evaluation and treatment of this disorder will be provided.

Pathophysiology and Links to Substance Use Disorders

Animal Models:

The idea that certain highly palatable foods containing sugar and/or fat have addictive properties was inspired by the behavioral criteria for substance use disorders that appear in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV-TR),[4] specifically tolerance, withdrawal, and loss of control. This idea was explored in a series of classic experiments carried out in the Hoebel laboratory at Princeton University, in which rats in an access/restriction group (12 h of access to both lab chow and a glucose/sucrose solution followed by 12 h of food deprivation) and controls (rats with *ad libitum* access to a sucrose solution or lab chow) were followed for 3 weeks. Compared to controls, animals in the access/restriction group exhibited binge usage (i.e., increased intake during the first hour of food exposure), spontaneous periods of binging during the time food was offered, an increased number of lever presses for sugar, and opioid-like withdrawal symptoms following sugar/chow removal or *naloxone* (Evzio) administration.[5, 6] Rats following a restricted intake paradigm (12 hours of deprivation followed by 12 hours of *ad libitum* access to food) demonstrated locomotor cross-sensitization to amphetamine and increased alcohol intake.[8, 9] A critical observation from these experiments is that unlimited access to food or sugar alone does not result in an addiction-like phenotype, but restricted access appears to be absolutely necessary for a behavioral change to occur.[5]

Studies have shown that when rats binge on sugar alone, they do not gain weight; when offered sugar and fat, however, they tend to binge and gain weight.[10] They have also shown that rats that binge on fat alone do not show symptoms of an opioid-like withdrawal syndrome when naloxone is administered,[11] but binge-prone rats tolerate high levels of shock when naloxone is administered with a food rich in both sugar and fat.[12] Additionally, Bocarsly and colleagues found that rats with access to solutions containing high-fructose corn syrup–one of the most common food additives used today[13]—demonstrate an increase in abdominal adiposity, weight gain, and hypertriglyceridemia.[14] Collectively, these preclinical findings suggest that individual macronutrients may selectively modulate addictive-like behaviors through both convergent and divergent mechanisms.[10, 11, 15] Because humans typically consume foods containing a multifarious array of nutrients, we can envisage a model in which foods rich in sugar and fat, such as those consumed in the so-called "western diet," interact with underlying genetic and environmental factors to result in a food addiction-obesity syndrome.[15]

Neurotransmitter Systems:

Many decades of research have implicated the neurotransmitter dopamine as being central to drug addiction, in terms of binging and intoxication (marked by an acute surge in striatal dopamine release in the nucleus accumbens with substance use), a withdrawal-negative effect (depletion of dopamine following cessation of substance use), and preoccupation/anticipation (dopamine release on anticipation of substance use or experience-associated salience).[16] Emerging evidence suggests that changes in dopamine release, receptor density, and receptor gene expression that are seen in drug addiction may underlie the manifestation of food-related addictive

behaviors in rats.[10, 17] Food intake results in the release of dopamine from the striatum. In rats exposed to food *ad libitum* after satiety has been achieved, however, the novelty of the food, even highly palatable food, wears off and dopamine release is blunted.[10, 17] In rats that binge on highly palatable food, dopamine release surges in the nucleus accumbens in a manner similar to that seen during binge-intoxication of drugs of abuse.[18] Downregulation of the *dopamine receptor D2* (D2R)—a consistent finding in addiction—is also seen in obese rats. Similarly, D2R knockout rats demonstrate compulsive food-seeking behaviors when exposed to highly palatable foods.[17]

The endogenous opioid system also appears to play an important role in the overconsumption of highly palatable foods and food addiction. In murine models, binge-like consumption of highly palatable foods is associated with increased expression of the *mu-opioid receptor* (MOR) in the cingulate cortex, hippocampus, locus coeruleus, and shell of the nucleus accumbens—key areas involved in emotion, memory, and the stress response that have similarly been implicated in addiction.[2, 5] A variety of MOR agonists has been associated with an increased intake of highly palatable foods, particularly in binge-eating animals; conversely, MOR antagonists such as naltrexone have been associated with a decrease in binge eating of highly palatable foods.[2, 5] As mentioned previously, administration of the MOR antagonist naloxone produces symptoms similar to those of opioid withdrawal in rats with a history of the binge eating of sugar.[5, 6]

Other Neurotransmitter Systems: Encocannabinoids, Orexin (CASA), Ghrelin, and Leptin:

The endocannabinoids comprise a complex neurotransmitter system that plays a key role in addiction to substances such as marijuana and alcohol, and marijuana itself binds to the CB1 receptor.[19] Additionally, the endocannabinoids are thought to modulate key neurotransmitters that affect appetite and satiety.[20] The CB1 receptor inverse agonist rimonabant was indeed shown to be efficacious for weight reduction in obese patients; however, adverse psychiatric side effects (including suicidal ideation) led to its withdrawal from the worldwide market.[3, 21] Orexin (or hypocretin), a neuropeptide that regulates arousal, appetitive, and feeding behavior, has also been implicated in cue-induced drug seeking.[22] Ghrelin (an orexigenic hormone) and leptin (an antiorexigenic hormone) are important regulators of appetite and are thought to play key roles in the reward valuation of food.[2]

Neuroimaging:

In healthy (non-obese) individuals, the ingestion of palatable foods results in the release of dopamine from the striatum in amounts proportional to the subjective rating of the food.[23] **Just as the ingestion of substances of abuse results in blunted activation of the reward circuitry in drug-addicted individuals, however, the ingestion highly palatable food results in blunted activation of reward circuitry in obese individuals.[16, 24] Additionally, exposure to highly palatable food (high fat/high sugar diets) is associated with downregulation of striatal D2Rs, decreased dopamine transporter expression and function, and decreased dopamine concentration in the nucleus accumbens.[24]** Collectively, these data support the "reward deficit" heuristics of both drug and food addictions: Changes in reward circuitry (a "less responsive system") underlie parallel changes in behavior in both drug use and binge eating, resulting in the individual transitioning from "impulsive" to "compulsive" use/eating.[25, 26]

Clinical Validity

The putative instrument for evaluating and diagnosing food addiction is the *Yale Food Addiction Scale* (YFAS), developed by Gearhardt, Corbin, and Brownwell in 2009. Development of the YFAS was inspired by the phenomenologic overlap of hedonic food consumption and drug/alcohol addiction and corresponding neurobiological underpinnings discovered in the preclinical models described earlier in this lesson.[27, 28] Gearhardt and colleagues developed and validated criteria based on *DSM-IV-TR* criteria for substance use disorders, emphasizing features such as tolerance, withdrawal, loss of control, and clinically significant impairment in function.[27, 28] The validity of the YFAS is also convergent with other measures of problematic eating and discriminant against a measure of alcoholism.[27] Gearhardt and colleagues added construct validity to the YFAS using BOLD (blood-oxygen-level dependent) contrast-based *functional magnetic resonance* (fMRI) imaging. Their

fMRI imaging study findings demonstrated that in both healthy and obese subjects, YFAS scores correlated with an increase in BOLD signaling in the anterior cingulate cortex, amygdala, and medial orbitofrontal cortex—areas that have consistently been shown to play a role in both drug addiction and feeding/appetitive motivation.[29] The YFAS has since been updated to reflect *DSM-5* criteria (YFAS 2.0),[30] and a version for children has been developed (YFAS-C).[31]

Epidemiology

Evidence of the prevalence of YFAS-defined food addiction is still somewhat preliminary;[3] however, in a survey of more than 130,000 women enrolled in the Nurses' Health Study, Flint and colleagues found that nearly 6% of women met YFAS-defined criteria for food addiction, with a positive relationship observed between higher body mass index and a diagnosis of food addiction.[32] Using much smaller, general population-based samples, one study found the prevalence of food addiction in overweight/obese subjects to be approximately 7%, whereas another found it to be approximately 15%.[33, 34] In a clinical sample of obese patients seeking bariatric weight loss surgery, nearly 54% met the criteria for food addiction.[35]

Delimitation from Eating Disorders

Eating disorders (including BED) and substance use disorders share phenomenological similarities, including loss of control, continued behavior despite negative consequences, cravings, and impulsivity.[36, 37] In eating disorders, however, the pathologic and diagnostic foci are on thought processes and self-valuation by the patient rather than on the food; whereas in substance use disorders, the substance itself is of capital importance.[3] This distinction represents the key delimitation between the two diagnostic categories, with food addiction representing a bridge between the two constructs, i.e., certain genetic vulnerabilities and neuroadaptive changes may represent an endophenotype of the food-addicted person, and certain characteristics of a given food (palatability, sugar content) may increase its addiction liability relative to other foods.[3]

Compared with individuals without BED, individuals with BED tend to meet the criteria for food addiction. Individuals with food addiction also tend to meet the criteria for BED compared with those who do not meet the criteria for food addiction.[3] Preliminary work shows that an even higher percentage of patients with *Bulimia Nervosa* (BN) meet YFAS criteria for comorbid food addiction than do patients with BED.[38] **Additionally, a bulk of evidence suggests that individuals with BED or BN who meet the criteria for food addiction appear to exhibit more severe food and eating-related pathology than individuals with BED or BN without comorbid food addiction.[3]**

Assessment and Diagnosis

Literature and guidelines on the evaluation and treatment of food addiction are limited in number. The actual prevalence of food addiction is unknown, given that more than 50% of obese patients may meet YFAS criteria for food addiction. Therefore, screening for food addiction in obese patients seen in primary care, as well as in psychiatric and other clinical settings, may be prudent.[3] Given the comorbidity of substance use disorders, eating disorders, and food addiction, we recommend evaluating patients with eating disorders for substance use disorders and vice versa.[3] Both of these patient groups should also be screened for food addiction.[3] Weight monitoring is a standard practice in the treatment of eating disorders, and we have suggested the same for patients in substance abuse treatment programs.[39, 40]

Treating Food Addiction

Behavioral Therapies:

If a diagnosis of food addiction is considered (as is standard with the evaluation and treatment of substance use disorders), a thorough psychiatric history should be taken and mental status examination performed, because failure to identify and treat a co-occurring psychiatric illness may worsen its prognosis.[3] Again, little evidence exists regarding treatment, but *cognitive behavioral therapy* (CBT) has been shown to be efficacious in the treatment of both BED and substance use disorders. Although it has yet to be investigated in patients with food addiction, a combination of CBT techniques for BED (with a focus on distorted body image) and substance use

Table 1:
Similarities and Differences among Food Addiction, Binge Eating Disorder, and Bulimia Nervosa

FOOD ADDICTION	BINGE EATING DISORDER	BULIMIA NERVOSA
Food taken in larger amounts and for longer periods than intended (loss of control)	Recurrent episodes of binge eating: • Large amounts • Lack of control	Recurrent episodes of binge eating: • Large amounts • Lack of control
Persistent desire/repeated unsuccessful attempts to quit or cut down	Unsuccessful attempts at controlling binging	Inappropriate compensatory behaviors (purging)
Cravings	Cravings	Body weight/shape influence self-evaluation
Much time/activity to obtain/eat/recover	Eating beyond satiety	
Important social/ occupational/recreational activities given up/reduced	Eating when not hungry	
Use continues despite knowledge of adverse consequences	Eating alone due to embarrassment of quantity eaten	
Tolerance	Feelings of disgust after binging	
Withdrawal		
Consumption causes clinically significant distress		

disorders (craving-focused coping skills) may be a useful intervention.[41]

Most accepted behavioral therapies for substance use disorders (including CBT) promote abstinence from drugs or alcohol. Unfortunately, strict avoidance of high-caloric "binge" foods may not be similarly helpful in patients with food addiction. **Extensive preclinical and clinical evidence has shown that substances of abuse have a "priming" effect in individuals with substance use disorders (i.e., index use promotes additional uncontrolled consumption); similarly, preclinical models have shown a priming effect for highly palatable foods in the promotion of binge eating.[41]** Clinical evidence indicates, however, that strict avoidance of "trigger" foods in BED may, in fact, result in more frequent binging.[41] More clinical evidence is needed to better elucidate the role of abstinence vs controlled eating in patients with food addiction.[3]

Pharmacotherapy:

A combination of *naltrexone* (Revia, Vivitrol) and *bupropion* (Wellbutrin, Aplenzin, Zyban) has been approved by the *US Food and Drug Administration* (FDA) for the treatment of obesity.[1] This combination might target pathways involved in the reward deficit (i.e., food addiction) model of obesity, which includes a bupropion-mediated attenuated hypothalamic response to food cues and enhanced activation of areas associated with inhibitory control (anterior cingulate cortex), internal awareness (superior frontal gyrus, insular cortex, and superior parietal lobe), and memory (hippocampus).[42] Additionally, preclinical work has shown that a high-dose baclofen-naltrexone combination results in a significant decrease in the consumption of highly palatable foods (compared with either the drug alone or a vehicle) without changing the consumption of standard laboratory

chow.[43] Rigorous testing in human populations would be required to determine whether this combination is useful in overcoming food addiction.

We note that these preclinical and clinical studies highlight superior efficacy and an increased response to combination pharmacotherapy rather than to a single agent. Addiction is a complex disease, affecting many neurotransmitter systems and an array of neural circuits.[16] In the case of food addiction, both preclinical and clinical evidence suggest that the different macronutrients in highly palatable foods may synergistically contribute to the development of a food addiction phenotype through both independent and overlapping mechanisms.[44] Thus, a single agent modulating a single neurotransmitter or targeting one neuropeptide would be expected to have marginal efficacy and a neuroscience-informed, multitargeted approach appears to be closer to ideal.

Policy and Public Health

Despite our focus on a neuroscience-informed and empirically validated approach to food addiction and treatment, the most effective interventions will likely be developed through public health policy efforts. Indeed, when looking at addiction treatment from a historical perspective, public health interventions have had the most dramatic effects on outcomes in every domain. For example, the 18th amendment, which banned the sale and distribution of alcohol ("Prohibition"), may have been short-lived and frequently presented as political mishap, but it was indeed a significant public health success. During its 13-year existence, rates of alcohol-related deaths and cirrhosis plummeted, as did admissions to institutions for alcohol-related psychosis.[45] Additionally, raising the drinking age to 21 and implementing drunk driving laws also resulted in many lives being saved.[45] Another great addiction-related public health success is the dramatic decline in smoking. The prevalence of cigarette smoking declined among American adults from more than 42% in 1965 to 15.1% in 2015.[46, 47] Many factors contributed to this successful outcome (with still more work to be done), with clean air laws, smoke-free restaurant mandates, and an increase in tobacco taxes truly being the driving forces behind it.[46]

Similar approaches have also been implemented to target obesity. In 2006, under the leadership of then Mayor Michael Bloomberg, New York City implemented a number of policies directed at reducing sugar consumption, including caloric and drink size restrictions. Along with an aggressive media campaign, these policies have effectively reduced sugar consumption in New York.[48] **Additionally, a number of municipalities and counties have instituted taxes on sodas and other sugary drinks. This has the potential to significantly reduce obesity through a net reduction in caloric consumption and increase obesity prevention program funding through the taxes themselves.[49]** Data on health outcomes specifically have not been gathered yet. When similar taxes were introduced in Mexico, however, sweetened beverage purchases decreased substantially. Thus, public health interventions implemented within a food addiction conceptual framework (i.e., interventions targeting access to and consumption of highly palatable foods) can have large-scale implications for developing policies that can address the obesity epidemic.

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Multiple-Choice Questions

9. Ms. Z, a 27-year-old obese woman with a history of stimulant use disorder presents for intake in a residential substance use disorder treatment facility. In addition to standard substance and psychiatric histories (including cursory screening for affective, psychotic, anxiety, and eating disorders), what scale might be useful in optimizing the physician's understanding of the patient's complete clinical picture?

A. *Beck Depression Inventory* (BDI)

B. *Yale Food Addiction Scale* (YFAS)

C. *Young Mania Rating Scale* (YMRS)

D. *Positive and Negative Syndrome Scale* (PANSS)

10. Upon evaluation, Ms. Z, described in the previous question, is found to have a prolonged history of binge-eating disorder and also meets criteria for food addiction. What will best characterize her eating behavior if it is not closely monitored?

A. Severe, unregulated binges on food

B. Self-starvation

C. Occasional binges

D. Isolated purging

11. Preclinical models have shown a _____ effect of highly palatable foods in the promotion of binge eating.

A. Priming

B. Shaming

C. Avoidance

D. None of the above

12. What public health intervention may prove most effective in addressing food addiction-related obesity?

A. Billboards and TV marketing ads describing food addiction

B. Subsidizing advertisers to use attractive, thin models to encourage weight loss

C. Mandating that all foods have a "fat-free" option

D. Taxing sugary beverages

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Best Practices in CME

Food Addiction

By A. Benjamin Srivastava, MD; Mark S. Gold, MD, DFASAM, DLFAPA

ID#: L003406

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.

Brief Lesson Overview:

This CME lesson will be helpful for psychiatrists and other physicians as a guide for the conceptualization, evaluation, and treatment of patients with food addiction.

Key Point 1: "Food Addiction" Posits a Causal Explanation for Obesity With Firm Preclinical and Clinical Support

In the context of the obesity epidemic, food addiction may be a valid explanation for the central nervous system pathology underlying the patient's weight problems. Decades of animal research and recent clinical findings provide support for food addiction as a disease.

Key Point 2: Food Addiction Represents a Bridge Between Substance Use Disorders and Eating Disorders

While some eating behaviors in the patient addicted to food may resemble bulimia nervosa or binge eating disorder, a crucial difference lies in the fact that the addictive behavior in food addiction is driven in part by the addictive properties of the food itself, in parallel with substance use disorders.

Key Point 3: Combined Approaches May Be the Best Solution

Given that most food contains many different micro- and macronutrients, some of which (e.g., glucose/sucrose) have addictive properties and lead to weight gain (e.g., trans and saturated fats), combination pharmacotherapy, in addition to psychotherapy, may be the most efficacious strategy for intervention. Although the data on neuromodulation are very preliminary, this may represent an important alternative avenue for intervention.

Key Point 4: Public Policy Implications

In the same way that cigarette taxes and clean air laws have largely driven the decrease in smoking prevalence in the United States, taxes and size restrictions on sugary beverages may reduce consumption and lead to overall reduction in the prevalence of illnesses such as diabetes and obesity.

Notes

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Core Clinical and Ethical Considerations for Psychiatrists Treating Transgender Persons and Persons With Intersex Conditions

Edmund G. Howe, MD, JD

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

KEY WORDS: Transgender • Intersex • Ethics • Gender identity • Psychiatry • Multidisciplinary approach

LEARNING OBJECTIVES: This lesson presents an overview of clinical considerations in the treatment of transgender persons and persons with intersex conditions. Readers will (1) review ethical problems that may arise in the treatment of transgender and intersex patients and optimal options for resolving them; (2) identify current theories regarding optimal approaches to infants born with intersex conditions; and (3) describe means of disclosing the genetic gender to children and adults when it differs from their previous understanding.

LESSON ABSTRACT: Transgender persons and persons with intersex conditions experience greater hardship than others in obtaining adequate and appropriate care in clinical settings. In particular, there is a lack of psychiatrists specializing in these two areas. Psychiatrists may have to address several difficult clinical and ethical questions to provide optimal treatment for these patients. This lesson discusses key considerations that psychiatrists should keep in mind when treating such individuals.

COMPETENCY AREAS: This lesson focuses on unique characteristics of transgender persons and persons with intersex conditions, as well as differences in their values, preferences, and expressed needs. It emphasizes optimal means of communicating with and educating these individuals, placing a priority on their identity and interpersonal quality of life. Professionalism is manifested through commitment to ethical principles and sensitivity to their diverse needs. This lesson presents information that is required to provide quality psychiatric care based on current standards of medical care.

Introduction

Transgender persons and persons with intersex conditions may pose several difficult clinical and ethical issues to the psychiatrist attempting to provide them with optimal care. Some difficulties can arise from the fact that persons born with intersex conditions are sometimes confused with transgender persons, although the two are wholly distinct from each other.

"People who identify as transgender or transsexual are usually people who are born with typical male or female anatomies but feel as though they've been born into the 'wrong body'." For example, a person who identifies as transgender or transsexual may have typical female anatomy but feel like a male and seek to become male by taking hormones or electing to have sex reassignment surgeries.

People who have intersex conditions have anatomies that are not considered typically male or female. Most people with intersex conditions come to medical attention because doctors or parents notice something unusual about their bodies. In contrast, people who are transgendered have an internal experience of gender identity that is different from most people."[1] The term "intersex" is used to refer to a variety of conditions in which the individual's reproductive or sexual anatomy lies outside the usual anatomic classifications of male and female, e.g., infants who are born with ambiguous genitalia. In contrast, research has shown that being transgender is most likely a result of a hormonal imbalance that develops in utero while the fetal brain is differentiating into a male or female brain. It has been shown that male and female brains have slight structural differences. The largest study to look at sex differences in brain anatomy found that women tend to have thicker cortices, whereas men have higher brain volumes. Indeed, Price finds some significant differences in the brains of men and women.[2]

This hypothesis is supported by autopsy studies, functional *magnetic resonance imaging* (MRI) scans, and *single-photon emission computed tomography* (SPECT) scans that have provided evidence suggesting that some people are born with a male brain and a female body or vice versa.[3]

Psychiatrists may believe they lack sufficient knowledge of the medical and psychological needs of transgender and intersex persons to provide them the care they need.[4, 5] They may feel particularly less confident with transgender persons, because these individuals have only recently begun to identify themselves publicly and indicate their own needs. Psychiatric services are sorely needed for this population, however, and for several reasons. First, the population in need is considerably large, given that approximately 25 million persons, or 0.3% to 0.9% of the world's population over the age of 15 years, identify themselves as transgender.[6] Second, many transgender individuals have had experiences that usually result in psychological trauma. According to one U.S. survey, for example, nearly half of these individuals have been sexually assaulted at some point in their lives, and their poverty level is almost three times that of the general population. Almost one-third of these individuals have been homeless at some time in their lives, 10% within the past year alone.[7]

Unfortunately, there is a relative lack of psychiatrists and other providers specializing in the treatment of these individuals. However, psychiatrists lacking specialized training in this area can still provide sufficient medical and psychotherapeutic support to help transgender and intersex individuals overcome personal difficulties. Therefore, there is no need for the psychiatrist to turn such patients away because of a perceived lack of knowledge and skill.[8] Indeed, the psychiatrist who has not had patients with such conditions previously may require only basic information—such as that which is provided in this lesson—to provide services that would be substantially beneficial for transgender patients and patients with intersex conditions. Even if the psychiatrist feels that the patient needs services s/he cannot provide at that time, the psychiatrist can always refer the patient to other specialists.[9] By seeking the help of providers in other specialties, the psychiatrist would provide the multidisciplinary approach that many of these patients need and which is currently considered, in many contexts, to be optimal, cutting-edge care.

This lesson explores three major aspects of psychiatric care for transgender persons: (1) core concepts of patient care; (2) psychiatric care for specific circumstances; and (3) the role of the psychiatrist as an advocate for transgender persons requiring additional services. This lesson also explores two important aspects of psychiatric care for persons with intersex conditions: (1) conflicts and

controversy that arise in determining the need for care; and (2) specific therapeutic approaches to children and adults with intersex conditions.

Transgender Persons: Core Concepts

Most transgender persons have two overriding concerns: (1) they want to live authentically in their current gender—i.e., the gender with which they identify—as opposed to the gender with which they were born; and (2) they want to interact with others as normally as possible and have others interact with them on the basis of what they say and do and who they are—not solely on the basis of how they appear.[10] They may seek hormonal therapy and surgery to accomplish this. They may also need additional interventions that affect their facial hair, voice, and even their chest contour. They will also need to have their psychiatrists refer to them by the correct name and pronoun, with the understanding that these may differ greatly among transgender individuals and that the name may change over time. This must be kept in mind as the psychiatrist considers all therapeutic options.

Using the Right Pronouns, Right Names, and Right Words:

It is important that psychiatrists use the right pronoun when speaking with the transgender individual.[7] This may be difficult for the psychiatrist who saw the individual before any aspect of the gender changing procedure was carried out and addressed that person as a member of the opposite sex in the past. The psychiatrist should keep in mind that the pronoun to be used during the current examination should correspond with the patient's current gender. The psychiatrist should also be aware that some transgender persons do not want to be considered either male or female, preferring to identify themselves as gender nonbinary, gender nonconforming, androgynous, gender queer, gender fluid, or agender. **Thus, the psychiatrist may want to ask the patient to indicate the terms by which the patient wants to be referred. If the psychiatrist inadvertently uses the wrong term, s/he should apologize and note the appropriate correction.**

Psychiatrists should also be especially careful to call transgender individuals by their preferred first name, keeping in mind that this may change as the individual transitions from one gender to another. Some psychiatrists, like other providers, believe that it is the transgender person's responsibility to tell the clinician if the name preference changes. This may be difficult for the less assertive patient, however. For this reason, it may be preferable for the psychiatrist to take the initiative and ask.

There are many ways in which psychiatrists may speak of transgender persons in the third person. "Trans" is a relatively new umbrella term that is used to refer to individuals with an atypical gender. F-to-M means female to male; M-to-F means the opposite. Some may refer to an F-to-M person as a trans-man and to an M-to-F person as a trans-woman, although others just want to be referred to as a man or a woman. "Cis" is a term used to indicate that one identifies with the gender with which he or she was born. Thus, "cis" is the opposite of "trans."[11] Again, it may be best for the psychiatrist to ask their patients to identify the terms they prefer to be used to describe them.

Differences Along a Spectrum:

Typically, the transgender individual wants to live as a person of the gender opposite to the one with which s/he was born. Psychiatrists should recognize, however, that the desires of these individuals will vary greatly. Some may not want to start (or stop) making changes in their bodies, whereas others may want to do the exact opposite; some may want to take hormones but do not want surgery; and still others may want to have surgery performed in the upper part of the body but not the lower part.[12]

Similarly, the sexual orientation of these individuals (i.e., the persons to whom they feel sexually attracted) may differ greatly.[13, 14] One person may be attracted to persons of the gender opposite the one with which they currently identify; others may be attracted to people of the same gender as the one with which they currently identify; others may be attracted to individuals of either gender, while still others will be attracted to neither gender. Additionally, their feelings of sexual attraction might change over time. Psychiatrists should raise the topic of sexual preference, which can be difficult for anyone to talk about, to allow the patient to discuss this topic with them.[13] They should include in the discussion the fact that their sexual interests may change over time, e.g., in response to the effects of the hormones they take.[9, 15, 16]

If they want more information about this than the psychiatrist can provide, the psychiatrist should refer them to other specialists.

Taking PrEP:

During a discussion of sexual interests, the psychiatrist might want to ask the patient about any interest in taking the *pre-exposure prophylactic* medication known as PrEP. This oral, fixed-dose, antiretroviral combination tablet containing *tenofovir* (Viread, Vemlidy), *disoproxil fumarate*, and *emtricitabine* (Emtriva) can reduce the incidence of HIV significantly in people who engage in unsafe sex.[17-20] It is particularly important for the psychiatrist to raise this question, because providers differ in their attitude toward prescribing this drug. It is much more expensive than condoms, and condoms offer greater protection. Furthermore, some providers may be afraid that patients who receive this medication will believe that they will be at a lower risk of acquiring HIV and, consequently, will start engaging in unprotected sex or engage in it more often.[21] By contrast, individuals who want PreEP may be afraid to ask their providers for a prescription, because they believe their providers will think they want to engage in unsafe sex and will have negative feelings toward them.

The extent to which individuals using PrEP engage in unsafe sex is uncertain.[22] Consequently, the provider's decision to prescribe it may depend on the extent to which the provider respects the patient's wishes or wants to protect that individual from the results of his/her behaviors by refusing to prescribe it. The possibility that the transgender person's sexual orientation will change over time in response to hormone therapy and will affect the need for PrEP may involve medical knowledge that the treating psychiatrist does not have. In fact, the transgender person may know more about this aspect of treatment than the psychiatrist. Still, psychiatrists should not allow their lack of knowledge about the medical treatment of transgender persons deter them from seeing transgender patients and offering them all the help that they can provide.

Confidentiality:

Transgender persons may differ from many other patients in that they may, under some circumstances, not want their providers to know they are transgender. By contrast, providers tend to assume, for good reason that their patients will share with them private details about their lives. The psychiatrist may want to respect the wishes of their transgender patients and keep their transgender status confidential. **For this reason, the psychiatrist should ideally only record information in the patient's chart that was previously approved by the patient.[23] To ensure that the chart only contains information the patient wants others to see, the psychiatrist should tell the patient what s/he plans to write in the chart in advance so the patient can indicate any desired changes.**

Showing Transgender Persons Respect:

As with every other patient, it is of the utmost importance that the psychiatrist convey to transgender patients the utmost respect, both verbally and nonverbally.[24] This is particularly important for these individuals, because they may not receive such respect from many other people.[25] Psychiatrists may understand the physiological aspects of being transgender but may have attitudes that prevent them from showing transgender individuals as much respect as they show other patients. For example, some hold religious beliefs that make it difficult for them to accept an individual's decision to change gender.[26] Such psychiatrists may struggle with what they should do.[27] They may believe that they should treat the transgender patient, but they may not feel that they can be of any benefit to these patients because of their negative feelings toward them. **Psychiatrists who want to change their feelings toward transgender individuals may benefit from simply getting to know them better—i.e., seeing them as patients. It may even be helpful if they shared their misgivings with the patient during their first session. They can also let the patient know that if their admission makes the transgender individual uncomfortable, they are willing to refer them to another psychiatrist.**

Transgender Persons: Practical Medical Considerations

There are many practical considerations about the medical and psychological needs of transgender persons of which the treating psychiatrist should be aware. These include the need to (1) help transgender individuals decide whether to have surgery and when; (2) help transgender

individuals obtain other medical interventions they may need or want; and (3) help transgender individuals decide if they want to freeze and save their sperm or eggs before taking hormones.

Medical Needs:

Whether and When to Consider Surgery

Guidelines for surgery for transgender persons may depend on individual circumstances. **A common guideline is the length of time the individual has lived as a person of the gender with which s/he now identifies. This will enable that individual to determine whether s/he is as certain as possible about the desire to undergo the surgical procedures (many of which are irreversible) necessary to achieve the desired physical changes.**[28, 29, 30] Some of these persons may face circumstances that made the time spent in their gender identity of choice more difficult. A psychiatrist can help such individuals decide whether the length of time spent in the new gender has been sufficient, keeping in mind that some transgender persons have lived in the new gender for a considerable length of time before their first meeting with a psychiatrist. The psychiatrist can help them decide whether they are ready to proceed with treatment with hormones that can prevent the development of secondary sexual characteristics (if they are children or young adolescents) or treatment with hormones and surgical procedures that can help them achieve the desired physical effects (if they are already sexually mature), e.g., breast growth, decreased testicular volume, and decreased spontaneous erections in trans-women and cessation of menses, breast atrophy, clitoral enlargement, and voice deepening in trans-men.

Adults usually do not change their minds after having made gender-changing bodily changes. It is particularly difficult for psychiatrists and other providers to advocate for such interventions in young adolescents. One of the major considerations in this decision is that children through early adolescence who feel that they want to change their gender are likely to change their mind. In the latest (seventh) edition of the *World Professional Association for Transgender Health* (WPATH), published in 2012, the authors indicate that gender dysphoria in childhood does not inevitably continue into adulthood, noting that it persists in only 6% to 23% of boys and 12% to 20% of girls seen in gender clinics.[31] Adolescents who desire to change their gender usually request medications that can bring about the desired physical changes; during early adolescence, they may ask for medications that can prevent the development of secondary sexual characteristics. Expectedly, those who want to be trans-women want to prevent the development of a prominent Adam's apple, facial hair, or a deeper voice, and those wanting to be trans-men want to prevent the development of prominent breasts.

Gender-affirming hormonal therapy is usually initiated in adolescents when they appear to be competent to give informed consent, which is usually at the age of 16 years or older, although there may be compelling reasons to initiate such treatment at a younger age.[32, 33] Most transgender persons do not choose gender-affirming surgery, however, most often because of a lack of insurance coverage and inability to pay.[34] Additionally, surgery may be contraindicated because of a preexisting medical illness and/or fear of the loss of employment or the support of family or friends.[3, 34]

The best approach to younger individuals who express a desire to change their gender is to encourage them to allow more time so that they can better determine what is best for them. This may be especially important, given the limited amount of research that has been carried out in this area.[34] Providers should be particularly cautious when the desired interventions are irreversible. An approach exemplifying this principle, which originated in a California clinic, supports a child socially in his or her transgendered role without medical or surgical intervention, but it also suppresses puberty. This approach, which originated at the VU University Medical Center Amsterdam, is based on two decades of research and practice. It assumes that it is better not to actively transition a child socially but to remain neutral to the way in which the child expresses gender identity. If children persist into late adolescence in this model, they are assisted in transitioning. If not, they are supported socially as they adjust to their natal gender. Puberty may sometimes have to be suppressed until the choice between these two paths has been made.

An approach originating at the Child and Adolescent Gender Center Clinic, which is affiliated with the University of California, San Francisco, supports a child socially in a cross-gendered role without medical or surgical intervention, but it suppresses puberty as well.[36]

Medicines that block puberty suppress the release of LH and FSH from the pituitary gland. This then stops testosterone from being released from the testes and estrogen from being released from the ovaries, which suppresses puberty.[37, 38]

The most commonly used puberty blocker is *leuprorelin*, (Lupron Depot). It is typically administered through a monthly injection in the thigh.[39]

Overall, puberty blockers are considered to be very safe. However, we are not sure whether puberty blockers have negative side effects on bone development and height. While the research done so far shows that the effects are minimal, the long-term effects of puberty blockers will not be known until the first patients who took them get older.

If one has a penis and later chooses to have surgery to create a vagina as an adult (vaginoplasty), starting puberty blockers early in puberty may make it impossible to undergo the vaginoplasty surgery that is most commonly used in Canada. There are alternative techniques available, such as the use of a skin graft or colon tissue.[37]

This approach is based on the presumption of an adult transgender outcome, that is, that the child will decide later what gender he or she is, when he or she is an adult, despite the absence of a way to predict its outcome.[40] Psychiatrists looking for the most recent standards for deciding when and how to treat transgender persons should consult the WPATH website (www.wpath.org), which offers optimal standards of care and updates them regularly.[31]

Other Medical Interventions for Transgender Persons

Transgender persons may have additional needs that are often associated with persistent undesired secondary sex characteristics. Men who transition to women may, for example, still have facial hair after hormonal therapy. If the facial hair grows every day, it may impair the individual's quality of life. Trans-men may also have to contend with a deep voice and trans-women with prominent breasts. These and other problems will need to be addressed.

Psychiatrists clearly should support these individuals in seeking the most desirable end results in any way possible. In one study, for example, ruminations—which serve as a marker of psychological distress—decreased in a transgender woman after surgery and after each additional procedure, as well.[41]

Freezing Sperm and Eggs Prior to Taking Hormones

If transgender persons take hormones over a long period of time, their ability to have children may eventually be adversely affected.[42] A psychiatrist may want to ask them if they want to freeze their sperm or eggs prior to taking hormones and save them for use in the future.[43-49]

Psychological Needs:

Psychiatrists who provide therapy or psychotropic medication for transgender persons should consider three things: (1) dysphoria in these individuals may develop as a result of feeling they are in the wrong body; (2) the patient may have a psychiatric disorder, such as depression, which should be identified and treated; and (3) both the psychiatrist and the patient may find that they are in a bind due to the psychiatrist having two roles, and the psychiatrist may want to discuss this conflict with the patient before it manifests itself. One role is as therapist. Another role is as a gatekeeper or provider who must approve hormone treatment or surgery before such treatments can be initiated. Since the transgender person may want hormones or surgery, when seeing the psychiatrist for therapy, if the psychiatrist is filling both roles, the transgender person may say what he or she thinks is most likely to obtain the psychiatrist's clearance for hormones or surgery, not what he or she genuinely feels. Thus, if the psychiatrist has both roles, this may undermine the patient's willingness to share what he or she truly feels, and thus, the success of the psychotherapy.

Dysphoria Versus Depression

These persons may have no physical disorders, but they may be experiencing anxiety and depression. Approximately 40% attempt to commit suicide.[26, 50, 51] Thus, they may need medication and/or psychotherapy. Some data exist that suggest that death by suicide and suicide attempts are much more common among individuals who have had sex reassignment surgery.[52, 53] However, a review of the consequences of sex reassignment in Europe found that suicide attempts and suicidal ideation may decrease from 20% before surgery to a much lower rate

(0.5–1.9%) after.[54] Most U.S. studies found that approximately 40% of LGB participants reported a lifetime history of suicidal ideation.[55] Moradi (2009) found that veterans who had disclosed their sexual orientation while in the military perceived higher social cohesion within their units. While this study did not assess suicide risk per se, increased social cohesion may be protective against self-directed violence, as social support has been found to be protective.[56, 57] Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us?[57]

Research suggests that autistic traits are seen more frequently in transgender individuals compared with non-transgender individuals.[58] Their emotional pain may result in whole or in part from feeling that they are in the wrong body. One transgender person described this dysphoria as follows: *"By the time I was in my 50s, my gender dysphoria—which previously would strike me for a period of unbearable hours, days, or even weeks but then would pass—had become constant. The condition was there when I awoke and lasted until I fell asleep. It was like a car alarm I was powerless to silence."*[3]

Neither the transgender person nor the treating psychiatrist may know the extent to which this feeling is actually dysphoria. Perhaps their dysphoric feelings will remit after they change their bodies. For example, the parents of a late adolescent male who had grown up as a female reported that their son had felt depressed since early childhood. Once he had surgery to remove the breast tissue that had accumulated during early puberty, he appeared to be happy for the first time in his life.

Some persons who want to change their gender may deny this desire. For example, some men who want to be women will pursue dangerous roles in an attempt to affirm their masculine identity. They may only become aware of their true feelings regarding their lack of comfort with their gender later in life.

Psychiatrists may be able to help many transgender persons by encouraging them to discuss the many stresses they may encounter in society.[59] A common source of stress is the need to continually ask themselves when, whether, and to whom they should disclose that they are transgender.

A Possible Role Conflict for the Psychiatrist

Psychiatrists who treat transgender persons using psychotherapy and/or medication may subsequently be asked by another provider, such as an endocrinologist or surgeon, to clear the patient for a different type of intervention, such as hormonal therapy or top or bottom surgery.[60] If the mental health provider has been treating the patient using psychotherapy, the decision to clear the patient may create an ethical conflict for both the patient and the psychiatrist. For example, if transgender individuals know in advance that a desirable procedure is possible, they may believe that they must choose between sharing their genuine feelings during therapy sessions or sharing what they believe will maximize the likelihood that the therapist will clear them for the medical intervention they want.[61]

Psychiatrists who anticipate this possibility can respond in any of several ways. They may decide to serve in only one capacity (i.e., as a therapist) for the patient. If so, they will inform any provider who requests clearance for the patient to have another procedure that they will not offer their recommendation. This should be done at the earliest time possible. This would mean deferring the decision-making role to another healthcare professional, which could result in the selection of suboptimal care, given that the other provider may not know the patient as well as the current treating psychiatrist. Alternatively, the psychiatrist may choose to share his/her personal dilemma with the patient so that together, they can arrive at a solution that works best for both of them—although the decision should be in the best interests of the patient.

Transgender Persons: The Psychiatrist as Advocate

There are numerous circumstances under which a psychiatrist should consider taking on the role of patient advocate. Doing so may go against the relatively traditional, psychodynamic psychiatric opinion that the psychiatrist should remain, essentially, neutral; however, it would allow psychiatrists to avoid compromising their ability to provide optimal psychotherapeutic care for their patients. The specific concern here is that the patient may expect the psychiatrist to eventually take on the role of advocate. This expectation may influence what patients say in

therapy as they attempt to encourage the psychiatrist to take on that role.

Psychiatrists who choose to serve as transgender patient advocates generally do so in one of three ways: (1) helping them acquire the medical interventions they need; (2) helping them freeze their sperm or eggs; or (3) enabling them to have and raise their own families.

Helping Transgender Persons Appear as They Are:

A primary objective of transgender persons is to appear to others in such a way that others do not respond to them first (or, ideally, ever) on the basis on how they look. A broad variety of medical interventions are available to help them achieve this goal. F-M trans-men, for example, may benefit from chest contouring surgery,[62] and M-F trans-women may benefit by having their voices changed to avoid being too deep, by eliminating facial hair, and with breast augmentation.[63]

Barriers to achieving this goal are gradually being torn down. For example, Medicare now covers hormone therapy and sex reassignment surgery for transgender people. Fifteen states and the District of Columbia forbid insurance exclusions that discriminate on the basis of gender identity. Eighteen states prohibit the abrogation of rights based on gender identity.[64] **Despite these advances toward equality, patients may still benefit from having a psychiatrist act on their behalf.**

Helping Transgender Persons Have and Raise Families:

Transgender persons often want to have a family, either through adoption or biologically. Their ability to do the latter may be medically problematic if they have been taking hormones for a relatively long period of time (e.g., more than a year), but it may still be possible. These patients may benefit from the advocacy of their psychiatrists as they attempt to obtain medical help.

Freezing and Storing Sperm and Eggs

As indicated previously, transgender persons who will be taking hormones may want to have their sperm or eggs frozen and saved for use in the future as a means of having a family.[65] The psychiatrist may be able to help them do this, again, by advocating for them.

Adoption

They may also encounter exceptional difficulties when they try to adopt children if the person who has a decision-making role in adoption cases believes that transgender individuals cannot be effective parents. Even when such individuals recognize this belief, they may give as their reason for rejecting a transgender applicant their belief that the transgender individual is suffering from depression. The psychiatrist who knows this is not the case should be willing to advocate on the patient's behalf.[66-69] Transgender persons may, in fact, be better parents than others,[70] given that the hardships they have faced may have allowed them to develop greater coping skills and resilience. Both of these qualities may enable them to feel greater empathy for their children and help them understand their children better. When their children hurt, they may be better able to help them cope.

Fortunately, beliefs regarding the parenting skills of transgender individuals are changing. In a recent divorce ruling, one court held that a nonbiological, nonadoptive partner should be granted both child visiting and custody privileges. The same court has said that the view that same-sex partners should not have equal family rights is currently "unsustainable."[71] Californians now have a third-gender option on their driver's licenses application and birth certificates. They can now state that they are "nonbinary." This is an umbrella term for persons who see themselves as falling outside male or female gender norms.[72]

Persons With Intersex Conditions

There are numerous causes of intersex conditions.[73] The best treatment depends on the specific condition and how it developed. Several other factors must be considered in all cases, however, including the following:[74] (1) parents should be cautious about approving surgery on their child's genitals to make them predominantly one gender or the other, because the surgery may be irreversible; (2) psychiatrists and other providers must consider how they will help affected children—and some adults—understand what their condition will mean for them; and (3) the parent, provider, and, sometimes, the child must determine whether such surgery actually should be done and, if so, when. A clinical approach to the *Complete*

Androgen Insensitivity Syndrome (CAIS) can be used as a paradigm for psychiatrists to decide how to inform a child or adult about his/her intersex condition.[75] Without careful thought about this intervention, the outcome for some children can be tragic.[76]

Surgery for Children With Intersex Conditions:

The question remains to this day whether children born with an intersex condition should have genital surgery,[77] which is performed to make the child's genitals female or male. Whether this question will even be raised may depend on the specific intersex condition that is present.[78] In the past, it was often assumed that surgery would result in the manifestation of the psychological make-up of the child as male or female, according to the surgery performed.[79, 80] In other words, it was believed that the child's gender identity would, over time, become the same as the gender of the "new" genitals. Sadly, this isn't always the case. **Now that providers realize this, they advise the parents of these children to consult a wide array of experts before making the decision to have surgery performed.[73]** Another commonly favored option is to wait until the child is old enough to participate in the decision-making process.

What to Say: CAIS as a Paradigmatic Example:

CAIS (formerly known as testicular feminization—a term that is no longer used because of the stigma associated with it) is characterized by an XY (male) karyotype in men whose cells are not responsive to testosterone. These men develop many female characteristics, which may include a shortened vagina. They do not have menses, however, and they cannot get pregnant. They may also have embryonic testicular remnants that can become cancerous if they are not removed.[81]

CAIS may first be identified during childhood or adulthood. If it is first identified during adulthood, the patient is probably not aware of its presence. Learning about it at that stage of life may be difficult for both the patient and her partner, because it indicates that the patient is of the opposite gender than they had believed. When psychiatrists and other providers first disclose this information to the patient, they must choose their words wisely. This task is even more important with children,[82] because they may be affected by the news more severely and for a longer period of time than if they heard it as an adult.

Telling Children About Their Intersex Condition:

When a psychiatrist is the first one to disclose to children with CAIS that they have this condition, or even if they talk with them later, it is critical to present the news in a way that leaves the children feeling good about themselves and their future. One provider's way of doing this is worth sharing:

After disclosing to a young girl that she has CAIS, this provider told her that her condition is like a pile of building blocks that like her are a girl but that this pile has merely been mislabeled. She then shows the girl a film in which two parents are pushing their child on a swing. All are quite obviously laughing. She then says that this is the future this girl can expect, though the child in this film is adopted. This second intervention is intended to convey to this child that she could look forward to having as happy a family life as anyone could, although she will not be able to have her own children.

Telling Adults About Their Intersex Condition:

The psychiatrist may be the first one to suspect or diagnose CAIS in adults.[35] These women may come with their husbands years, even decades, after they were married. They will, perhaps, only know that they have been unable to have children. When providers inform these women or couples that they have CAIS, they must do this with the same care they would use when they speak to a child. This wife and husband may face quite a challenge. The partner without CAIS must, for example, adjust to the new knowledge that the partner he thought was a woman is genetically a male.

It is worth noting that I have referred to women with CAIS unequivocally and only as women. Persons with CAIS are indeed women. This is the right and only word, along with related pronouns, that psychiatrists should ever use when speaking with or about these persons.

Conclusion

Psychiatrists and other practitioners should always be open to treating transgender individuals, offering them the benefit of their skills, regardless of how much experience and special expertise they believe they lack, and considering serving as their advocates whenever it may help. Individuals with intersex conditions can be assisted by urging the parents of children with one of these conditions to consult several experts from different disciplines before deciding whether or not their children should have surgery. They should also consider waiting until their children are old enough to participate in the decision-making process themselves. One approach to informing children with CAIS is provided as an example for explaining intersex conditions to affected children.

Psychiatrists should be willing to become as close as possible to persons in both of these groups in order to help them face the challenges that lie ahead and ensure optimal outcomes. The critical component of the therapeutic process for transgender individuals and person with intersex condition is the willingness of the psychiatrist to get to know these individuals and convey to them clearly that the psychiatrist really knows who they really *are*.

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Multiple-Choice Questions

13. You are speaking while doing therapy with a transgender person who has recently changed his gender. You refer to him as a "she" out of habit. What should you do?

A. Say nothing, expecting that this person hasn't noticed

B. Say nothing, to not risk adding to this person's discomfort

C. Chortle and say, "Bad me"

D. Apologize

14. You are seeing a transgender person for therapy. He tells you that he does not want other physicians he sees to know that he is transgender unless it is medically necessary. You should:

A. Inform him that doctors expect persons they see to tell them everything.

B. Ask him what he would like you to write in his chart and offer to have him review and alter what you plan on writing before you write it.

C. Inform him that doctors are or at least should be open-minded.

D. Ask him why this is so important to him.

15. A colleague says that he has value discomfort with persons changing their gender but would like to overcome this. He asks what you think he should do if a transgender person comes to him for treatment. You should:

A. Suggest that he disclose this and ask the transgender person if she would be willing to see him or would rather see someone else.

B. Tell him that his attitude is unprofessional.

C. Suggest he see this person without telling her.

D. Suggest he tell this to those who assign patients so that he will not face this conflict.

16. A transgender woman comes to see you because despite the hormones that she takes, she believes strangers stare at her because her body does not look like a woman's. She requests your support for her having breast augmentation. You should:

A. Give it.

B. Try to help her learn to ignore others' views.

C. Tell her that breast augmentation probably will not help her.

D. Sympathize with her but tell her that this would compromise your therapeutic neutrality.

Best Practices in CME

Core Clinical and Ethical Considerations for Psychiatrists Treating Transgender Persons and Persons With Intersex Conditions

By Edmund G. Howe, MD, JD

ID#: L003407

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Psychiatrists may encounter several difficult clinical and ethical questions in their efforts to provide transgender persons and persons with intersex conditions optimal treatment. This lesson discusses key considerations psychiatrists should keep in mind when they treat transgender persons and persons with intersex conditions. The willingness of psychiatrists to treat these individuals is exceptionally important, because these persons experience greater hardship than many others and there is a relative lack of psychiatrists specializing in these two areas.

Key Point 1: Verify Choices

Ask transgender patients if they would like to review and change what the psychiatrist will write in their chart before they write it.

Key Point 2: Duality of Roles

Anticipate the possibility of being asked to serve in two roles, namely as therapist and approval authority for desired treatments. Disclose and discuss this conflict with transgender persons when doing therapy to discern the transgender person's preference.

Key Point 3: Family Planning

Take the initiative to ask transgender persons who may take hormones whether they have an interest in pre-freezing and saving their eggs or sperm.

Key Point 4: Physician As Advocate

Act as advocates for transgender persons who want procedures such as chest contouring and breast augmentation to increase the quality of their interactions with others.

Key Point 5: Educate Parents of Intersex Children

Advise parents of infants with intersex conditions to consult with many experts from diverse disciplines prior to approving irreversible surgery for their child. Emphasize to children and adults who have intersex conditions that the gender with which they identify is their gender, not their genetic make-up.

Notes

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A Postal Survey of Doctors' Attitudes to Becoming Mentally Ill

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

KEY WORDS: Confidentiality • Disclosure • Doctors • Education • Mental illness • Psychiatry • Services • Stigma • Treatment

LEARNING OBJECTIVES: Upon completion of this lesson, clinicians will recognize the most prominent barriers to seeking care for and reporting mental illness and thus become more vigilant to overcome these barriers. Clinicians will gain knowledge that will help them foster an environment that does not stigmatize peers for seeking help. Lastly, this lesson will help equip readers to overcome the potential barriers by educating those in medical training and in practice.

LESSON ABSTRACT: A postal survey of 3,512 doctors in Birmingham was carried out to assess attitudes to becoming mentally ill. The response rate for the questionnaire was 70% (2,462 questionnaires). In total, 1,807 (73.4%) doctors would choose to disclose a mental illness to family and friends rather than to a professional. Career implications were cited by 800 (32.5%) respondents as the most frequent reason for failure to disclose. For outpatient treatment, 51.1% would seek formal professional advice. For inpatient treatment, 41.0% would choose a local private facility, with only 21.1% choosing a local NHS facility. Of respondents 12.4% indicated that they had experienced a mental illness. Stigma to mental health is prevalent among doctors. At present there are no clear guidelines for doctors to follow for mental healthcare. Confidential referral pathways to specialist psychiatric care for doctors and continuous education on the vulnerability of doctors to mental illness early on in medical training is crucial.

COMPETENCY AREAS: This lesson provides knowledge of identified barriers physicians reported in an assessment of their attitudes to becoming mentally ill. By identifying these potential barriers, clinicians can help create an environment that does not stigmatize help seeking, but rather encourages that healthy clinicians will have better outcomes in patient care.

Introduction

One in four people in the UK suffer from a mental illness.[1] Although doctors are generally physically healthier than the general population they have higher rates of mental illness and suicide.[2–4] Stigma to mental health and by extension to mental health services is a barrier for doctors being assessed and treated for a mental illness. With the adage 'doctors make the worst patients' this is an especially potent issue in spite of various anti-stigma campaigns. The literature in this area is primarily based on doctors with an active mental illness, substance misuse, anxiety and depression.[5–7] There are no studies encompassing all specialties that have sought doctors' views regarding disclosure and treatment if they became mentally ill. For this study the views of doctors on the prevalence of mental illness, their preference for disclosure, and treatment should they develop a mental illness in addition to their own experiences of mental illness were studied.

Participants and Methods

A confidential questionnaire was sent to all 3,512 doctors identified as working in the major teaching hospitals and general practice surgeries in Birmingham. The mailing list was obtained from each hospital's medical staffing department. The nine-item questionnaire was based on a review of the literature, discussion with colleagues and a pilot study. It comprised broadly of three sections. The first collected information on the respondents' perception of prevalence of mental illness in doctors in comparison to the general population and then in comparison with psychiatrists. The second required doctors to identify to whom they were most likely to disclose a mental illness. The third asked doctors their preference of treatment in both an outpatient and inpatient setting. The identifiable information requested was the grade of the doctor and whether they had experienced mental illness in the past. A free-text box was included at the end for comments and complete anonymity was maintained.

Statistical Analysis

A series of two-sample chi-square tests (χ^2) were carried out to examine association between certain categorical variables. Phi (φ) was used as a measure of effect size.

Results

Of the 3,512 questionnaires sent to doctors, 2,462 were returned (response rate 70.1%). The respondents comprised 677 (27.5%) consultants, 273 (11.1%) *specialist registrars* (SpRs), 441 (17.9%) senior house officers (SHOs), 542 (22.0%) *general practitioners* (GPs), and 529 (21.5%) doctors who classed themselves as 'other'.

Perception of Prevalence of Mental Illness in Doctors:

Of the respondents, 634 (25.8%) felt the prevalence of psychiatric illness in doctors was higher than that of the general population. Only 153 (6.2%) respondents felt that psychiatric illness was more prevalent than that of psychiatrists. A mental illness was reported to have been experienced by 306 doctors (12.4%). There was little difference between the non-psychiatrists and psychiatrists when estimating incidence of mental illness in doctors compared to the general population (Table 1). Only 6.2% of doctors thought that mental illness was more prevalent in their own specialty compared to psychiatrists. Conversely, 33.6% of psychiatrists thought that mental illness in their profession was higher than that of other specialties. As can be seen from Table 1, psychiatrists were slightly more likely to report having experienced mental illness (χ^2=24.66; df=1; p=0.001; φ=0.094).

Disclosure of One's Mental Illness:

The majority of doctors, 1,807 (73.4%), were most likely to disclose their mental illness to their family or friends; 317 (12.9%) to a professional/governmental institution; 159 (6.5%) to their colleagues; and 178 (7.2%) would not choose to disclose the illness. The most important factor for doctors that would affect their decision to disclose their mental illness was career implications in 800 (32.5%), professional integrity 731 (29.7%), stigma 489 (19.9%), and 'other' reasons 442 (18.0%).

Consultants were more likely than any other group to put forward professional integrity as the factor influencing disclosure. SHOs were less likely to disclose mental illness to colleagues or professional/governmental institutions and were more likely to tell family or friends compared with consultants and GPs (χ^2=107.1; df=12; p=0.001; φ= 0.21). SHOs were also more likely to cite

Table 1:
Comparisons Between Non-Psychiatrists and Psychiatrists On All Questions

		Non-psychiatrists (%)	Psychiatrists (%)
Q1. Are you a…	Consultant	677 (27.5)	195 (52.7)
	SpR	273 (11.1)	42 (11.4)
	SHO	441 (17.9)	102 (27.6)
	GP	542 (22.0)	
	Other	529 (21.5)	31 (8.4)
Q2. Incidence higher in doctors than general population?	Yes	634 (25.8)	124 (33.6)
	No	1,180 (47.9)	153 (41.5)
	Don't know	648 (26.3)	92 (24.9)
Q3a. Incidence higher in medical/surgical professionals than psychiatrists?	Yes	153 (6.2)	
	No	1,331 (54.1)	
	Don't know	978 (39.7)	
Q3b. Incidence higher in psychiatrists than other specialties? (This was asked in previous study involving psychiatrists only)	Yes		135 (36.6)
	No		121 (32.8)
	Don't know		113(30.6)
Q4. If you were to develop an illness, to whom most likely to disclose?	Family/friends	1,807 (73.4)	231 (64.9)
	Colleagues	159 (6.5)	49 (13.8)
	Professional/governmental institutions	318 (12.9)	45 (12.6)
	None	178 (7.2)	31 (8.7)
Q5. What is the most important factor that would affect your decision to disclose your mental illness?	Stigma	489 (19.9)	80 (22.4)
	Career implications	800 (32.5)	124 (34.7)
	Professional integrity	731 (29.7)	98 (7.5)
	Other	442 (18.0)	55 (15.4)
Q6. If you were to suffer a mental illness requiring outpatient treatment, what would be your first treatment preference?	Informal advice	1,000 (40.6)	114 (30.9)
	Formal advice	1,259 (51.1)	162 (43.9)
	Self-medication	119 (4.8)	73 (19.8)
	No treatment	84 (3.4)	20 (5.4)
Q7. If you were to develop a mental illness requiring inpatient treatment, where would be your first preference?	Local NHS	520 (21.1)	15 (4.1)
	Distant NHS	474 (19.3)	70 (19.1)
	Local private	1,010 (41.0)	169 (46.2)
	Distant private	458 (18.6)	112 (30.6)
Q8. In choosing the place of treatment in Question 7, which of the following influenced your decision most.	Quality of care	618 (25.1)	59 (16.3)
	Convenience	503 (20.4)	31 (8.6)
	Confidentiality	1,256 (51.0)	31 (8.6)
	Stigma	85 (3.5)	32 (8.9)
Q9. Have you ever experienced a mental illness?	Yes	306 (12.4)	81. (22.0)
	No	2,156 (87.6)	288 (78.0)

GP = general practitioner; SHO = senior house officer; SpR = specialist registrar.

stigma and career implications as the main influence on their choice to disclose than both consultants and GPs (χ^2=92.3; df=12; p=0.001; φ=0.19).

Table 2 shows doctors' choices for disclosure and the factors which influenced their choices. The modal choice for disclosure was family/friends and of those who would prefer this, the majority voiced concerns about career implications and professional integrity.

There were no significant differences between the non-psychiatrists and psychiatrists (Table 1) about to whom they would disclose their mental illness.

Treatment of Mental Illness:

Informal advice for outpatient treatment was selected by 1,000 (40.6%) respondents, 1,259 (51.1%) chose formal advice, 119 (4.8%) would self-medicate and 84 (3.4%) opted for no treatment. There was no significant difference between the different grades of doctor in their choice of outpatient treatment for mental illness.

In the event of developing a mental illness requiring inpatient treatment 1,010 (41.0%) doctors would opt for a local private facility; 520 (21.1%) responders would choose a local NHS mental health hospital; 474 (19.3%) would choose a distant NHS mental health hospital; and 458 (18.6%) would go to a distant private hospital. **As can be seen, the majority of those who chose a distant NHS hospital or a distant private facility were motivated by confidentiality; almost half of those who chose a local private hospital were influenced by confidentiality** (χ^2=967.9; df=9; p=0.001; φ=0.63). Interestingly only 618 (25.1%) would make the decision based on the best quality of care available (Table 3).

In the event of requiring inpatient treatment for mental illness, a local private facility was preferred by all groups (particularly by GPs) apart from SHOs (as shown in Table 4) who were the only group to prefer a distant private facility over all other options. When making decisions on inpatient treatment, 63.7% of SHOs were influenced by confidentiality or stigma as opposed to only 45.1% of consultants (χ^2=208.9; df=12; p=0.001; φ=0.29) (Table 5). The majority of the senior doctors (consultants, SpRs and GPs), were more likely to cite quality of care and convenience compared to junior doctors (χ^2=67.52; df=12; p=0.001; φ=0.159).

However, when compared to psychiatrists, non-psychiatrists were more likely to choose informal or formal professional advice and were less likely to self-medicate (χ^2=120.33; df=3; p=0.001; φ=0.206) if they experienced a mental illness requiring outpatient treatment. If inpatient treatment was required for mental illness, non-psychiatrists were more likely to choose a local NHS hospital and less likely to choose a distant private facility than psychiatrists (χ^2=73.6; df=3; p=0.001; φ=0.161). However, for both groups a local private hospital was the most popular choice. When asked what would influence the decision about inpatient treatment, nonpsychiatrists were more likely to cite quality of care and convenience than psychiatrists and less likely to cite confidentiality and stigma (χ^2=69.38; df=3; p=0.001; φ=0.157), although confidentiality was still the biggest influence for both groups.

Doctors who had experienced mental illness were more likely to prefer formal over informal advice for outpatient treatment (χ^2=29.76; df=3; p=0.001; φ=0.110). This group also preferred to be treated in a local NHS hospital compared to a distant NHS hospital for inpatient treatment. These doctors were less likely to cite confidentiality as influencing their decision over inpatient treatment (χ^2=27.12; df=3; p=0.001; φ=0.105).

Discussion:

This is the first large-scale study to investigate the views of non-psychiatrist UK doctors on disclosure and treatment preferences in the event of them becoming mentally ill. It was carried out in one city (Birmingham) and covered all specialties. Although generalizability of the results cannot be assumed, the high response rate (70%) and open text comments confirmed the importance of this issue to the participants. There is scope for more research in this field especially among other healthcare professionals.

Doctors have higher morbidity for depression and substance misuse as well as higher rates of suicide than the general population.[2–4] In this study, 12% of doctors reported having experienced a mental illness and the *British Medical Association* (BMA) estimates that 1 in 15 doctors will have a problem with alcohol or drugs at some point in their lives.[8] The training involved to become a doctor is associated with psychiatric morbidity in medical students and few seek help because of the stigma that it may affect their career progression.[9,10]

Despite the term 'stigma' dating back to the medieval ages its relevance to mental illness in 21st-century Britain is all too familiar. The media have at times addressed this

Table 2:
Doctors' Preference for Disclosure About Mental Illness and the Factors Which Influenced Their Choices

	Stigma (%)	Career implications (%)	Professional integrity (%)	Other (%)	Total (%)
Family/friends	381 (21.1)	618 (34.2)	483 (26.7)	325 (18.0)	1807 (100.0)
Colleagues	17 (10.7)	51 (32.1)	76 (47.8)	15 (9.4)	159 (100.0)
Professional / governmental institutions	30 (9.4)	96 (30.2)	137 (43.1)	55 (17.3)	318 (100.0)
No one	61 (34.3)	35 (19.7)	35 (19.7)	47 (26.4)	178 (100.0)
Total	489 (19.9)	800 (32.5)	731 (29.7)	442 (18.0)	2462 (100.0)

Table 3:
Doctors' Preference for Inpatient Care for Mental Illness and the Main Reason for Their Choice

	Quality of care (%)	Convenience (%)	Confidentiality (%)	Stigma (%)	Total (%)
Local NHS	221 (42.5)	273 (52.5)	24 (4.6)	2 (0.4)	520 (100.0)
Distant NHS	48 (10.1)	12 (2.5)	389 (82.1)	25 (5.3)	474 (100.0)
Local private	282 (27.9)	217 (21.5)	482 (47.7)	29 (2.9)	1010 (100.0)
Distant private	67 (14.6)	1 (0.2)	361 (78.8)	29 (6.3)	458 (100.0)
Total	618 (25.1)	503 (20.4)	1,256 (51.0)	85 (3.5)	2,462 (100.0)

issue unsympathetically with crimes committed by people with mental illness prioritized in the news and the dramatization of the 'sectioning' of celebrities under the Mental Health Act. Attempts have been made to address stigma including the Changing Minds campaign by the Royal College of Psychiatrists and the Department of Health's Action on Stigma.[11, 12] Over three quarters of doctors who cited stigma as a factor influencing their decision to disclose a mental illness would do so first to family or friends rather than to a professional. This was highlighted in the case of Dr. Daksha Emson who suffered with a mental illness and battled with stigma throughout her career in psychiatry, which ended prematurely with her taking her own life.[13]

Disclosing one's mental illness to a GP should, ideally, be a straightforward decision for doctors to make. Traditionally, doctors have avoided mental health services due to attitudes formed in medical school, a perceived lesser importance of mental health as well as a tendency to treat oneself.[14] Doctors also tend to be unsure about mental health and are less likely to recognize a problem, not only among themselves but also in their colleagues. This leads to gross underreporting and thus potential worsening of the illness.[15] Only 12.9% of respondents would disclose their illness to a professional, citing career implications and professional integrity as being the main reasons. This often results in the majority of doctors presenting late to mental health services putting themselves, and by extension their patients, at risk. If a doctor is suspected of impaired fitness to practice the *General Medical Council* (GMC) have clear guidelines, which advise how doctors can report their colleagues, if required. The culture of medicine encourages an image of invincibility and denial of vulnerability to illness creating a barrier to doctors seeking healthcare guidance. Options for doctors who feel they are mentally unwell are lacking.

Doctors suffering from stress and its related problems can access confidential counselling support for example, the BMA help line, Doctors Support Network and National Counselling Service for Sick Doctors. Specialist psychiatric help by local mental health teams can be accessed via a GP or occupational health department.

Table 4:
Preference for Inpatient Care for Mental Illness As A Function of Grade/Level

	Local NHS (%)	Distant NHS (%)	Local private (%)	Distant private (%)	Total
Consultant	224 (33.1)	94 (13.9)	282 (41.7)	77 (11.4)	677 (100.0)
SpR	65 (23.8)	63 (23.1)	104 (38.1)	41 (15.0)	273 (100.0)
SHO	73 (16.6)	108 (24.5)	114 (25.9)	146 (33.1)	441 (100.0)
GP	72 (13.3)	114 (21.0)	275 (50.7)	81 (14.9)	542 (100.0)
Other	86 (16.3)	95 (18.0)	235 (44.4)	113 (21.4)	529 (100.0)
Total	520 (21.1)	474 (19.3)	1,010 (41.0)	458 (18.6)	2,462 (100.0)

GP = general practitioner; SHO = senior house officer; SpR = specialist registrar.

Table 5.
Factors affecting preference for inpatient care as a function of grade/level.

	Quality of care (%)	Convenience (%)	Confidentiality (%)	Stigma (%)	Total
Consultant	193 (28.5)	179 (26.4)	285 (42.1)	20 (3.0)	677 (100.0)
SpR	69 (25.3)	56 (20.5)	143 (52.4)	5 (1.8)	273 (100.0)
SHO	106 (24.0)	54 (12.2)	253 (57.4)	28 (6.3)	441 (100.0)
GP	135 (24.9)	108 (19.9)	282 (52.0)	17 (3.1)	542 (100.0)
Other	115 (21.7)	106 (20.0)	293 (55.4)	15 (2.8)	529 (100.0)
Total	618 (25.1)	503 (20.4)	1,256 (51.0)	85 (3.5)	2,462 (100.0)

GP = general practitioner; SHO = senior house officer; SpR = specialist registrar.

Only half of all doctors requiring outpatient intervention would seek formal psychiatric advice and an even smaller number would opt for informal advice. The failure to seek appropriate help when ill is prevalent among the wider medical profession.[16] Issues of trust and concerns about confidentiality may act as barriers to medical practitioners seeking help for psychiatric illness.[17]

One of the most important factors influencing where a doctor is treated is the issue of confidentiality. Despite confidentiality being a principal factor for maintaining trust within the medical profession, this does not seem to correlate with the results of this study. There seems to be no confidence among doctors that their mental health data will remain confidential. This may imply that doctors lack confidence in the current system and raises the question, how confidential is confidentiality? The current practice in the UK of keeping electronic records means that hospitals are intra-connected with numerous computers. This increases the potential of people accessing other colleagues' personal information. This lack of confidence in confidentiality may explain the trends in doctors self-medicating with alcohol and substance misuse.

The results show that psychiatrists are more likely to feel a greater burden of stigma compared to their non-psychiatrist colleagues. This is surprising as one would expect psychiatrists to be tackling stigma on a daily basis. On the surface it would seem psychiatrists are not practicing what they preach. It was also found that psychiatrists are more likely to experience a mental illness at some point in their lives. However, this may be due to the fact that non-psychiatrists are not disclosing their mental illness or are failing to recognize it.[18]

A text box was provided for free comments at the end of the questionnaire. It was interesting to note that, of the doctors who 'had' experienced a mental illness and been in touch with local mental health services, they generally reported a very positive experience. However some did report that if an option of a specialist unit for doctors

'did' exist, this would be the first choice. A key issue of confidentiality will still remain. Some may also argue that the very existence of separate specialized units adds to the problem of stigma.

Strengths and Weaknesses

This study addresses an important issue and includes a unique insight of doctors' views towards mental health. The large sample size added to the strength of the study and the high response rate confirmed the importance given to this topic by the doctors involved. The study could have been expanded to include gender and subspecialty. Specific mental illnesses could have also been examined. The study could also be expanded to include other mental healthcare professionals.

Conclusion

Education on stigma and its consequences should be made more prominent in medical schools and training courses for junior doctors. So far anti-stigma campaigns have targeted a large audience. Studies have shown that smaller campaigns that are targeted towards specific groups are much more successful.[19] Junior doctors are receptive to education on physician impairment and substance misuse and this should be a mandatory component of their training.[20] Further education is required on training medical students and doctors on how to detect mental illness at an early stage. The medical school curriculum could incorporate training on consultation skills for situations in which the patient is also a doctor.

A greater emphasis is required to educate doctors on mental health and the provision of an option to confidentially refer themselves to mental health teams. Doctors are reluctant to utilize occupational health services for fear that they will be seen as a problem that is best removed rather than rehabilitated. Similarly with the GMC, the association of reporting mentally ill doctors with disciplinary measures could be revisited with a separate more humanistic approach – a return to the previous system. Trusts should develop clear protocols for the records of healthcare professionals and access should potentially be restricted. The common pathway into NHS psychiatric services remains via the GP which, according to this study, most doctors may avoid.

The concept of stigma to mental illness is one that has evolved over time and will require a consistent and long-haul effort to tackle if doctors are expected to gain the confidence to ask for and accept psychiatric help. This research clearly shows that doctors are concerned about confidentiality and stigma and a medical service is required which meets their needs. Consideration should be given to the establishment of regional assessment and treatment services. One of the authors (AW) currently provides an occupational health psychiatric session based in the occupational health department. If such fully funded and well advertised sessions were available to doctors on a regional basis it could provide the necessary ease of accessibility accompanied by confidentiality. Additional access to psychological therapies and local private inpatient care should encourage psychiatrically ill doctors to seek treatment therefore reducing the risk to themselves and in turn to their patients.

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L003408

Multiple-Choice Questions

17. For treatment of mental illness, which of the following was selected by the highest percentage of responding doctors?

A. Informal advice for outpatient treatment

B. Formal advice

C. Self-medication

D. No treatment

18. In the event of developing a mental illness requiring inpatient treatment, which deciding factor was seen as being most important to the responding doctors?

A. Confidentiality

B. Quality of care

C. Convenience

D. Stigma

19. Doctors have higher morbidity for depression and substance misuse as well as higher rates of suicide than the general population. This statement is:

A. True.

B. False.

20. According to the lesson, what percentage of respondents would disclose their illness to a professional, citing career implications and professional integrity as being the main reasons?

A. 2.9%

B. 12.9%

C. 22.9%

D. 32.9%

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Best Practices in CME

A Postal Survey of Doctors' Attitudes to Becoming Mentally Ill

By Tariq M. Hassan, MBBS, MRCPsych (UK), FRCP(C); Syed O. Ahmed, MBBS, MRCPsych;
Alfred C. White, MD, FRCPsych; Niall Galbraith, PhD

ID#: L003408

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.

Brief Lesson Overview:

Stigma to mental health is prevalent among doctors. At present there are no clear guidelines for doctors to follow for mental healthcare. Confidential referral pathways to specialist psychiatric care for doctors and continuous education on the vulnerability of doctors to mental illness early on in medical training is crucial.

Key Point 1: The Barrier to Seeking Help

Stigma to mental health and by extension to mental health services is a barrier for doctors being assessed and treated for a mental illness. The overarching concern expressed in this study was confidentiality.

Key Point 2: Study Findings on Disclosure of Mental Illness

The most important factor for doctors that would affect their decision to disclose their mental illness was career implications. Doctors reported that their primary choice for disclosure was family and friends, rather than report to a colleague or institution.

Key Point 3: Future Direction to Overcome Barriers

Education on stigma and its consequences should be made more prominent in medical schools and training courses for junior doctors. Similarly, medical school curriculums need more education on how to detect mental illness at an early stage even amongst their peers.

Notes

L003409

hatherleigh

The Mentally Disordered Offender's Path Within the California Correctional System: California's Mentally Disordered Offender Act

Juliana Rohrer, PhD; Jeff Kropf, PhD

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

KEY WORDS: Mentally disordered offender • Forensic mental health evaluation • Involuntary hospitalization

LEARNING OBJECTIVES: Upon completing this lesson, the clinician will be able to (1) assess the applicability of the *Mentally Disordered Offender* (MDO) Act to individual inmate/patients; (2) formulate opinions regarding the applicability of the six statutory criteria for MDO status to individual inmate/patients; (3) offer and defend informed opinions regarding the applicability of the six statutory criteria in legal hearings and trials.

LESSON ABSTRACT: The MDO Act of California allows for the potentially involuntary placement of prisoners in a state hospital for mental health treatment at the time of their scheduled release from prison. This lesson discusses the issue of involuntary psychiatric hospitalization, the genesis of the MDO Act and the MDO Unit of the California Department of State Hospitals, statutory parameters that allow the potentially involuntary hospitalization of prisoners (as set forth by the MDO Act), and the processes of identifying, evaluating, and certifying a prisoner as an MDO.

COMPETENCY STATEMENT: This lesson enables clinicians to employ evidence-based practice and integrate clinical expertise and patient values by examining California's MDO statute. The lesson provides information regarding the history, intent, and application of the MDO statute aiding them in conducting ethical and responsible forensic mental health evaluations and research activities.

Introduction

The *Mentally Disordered Offender* (MDO) Act, codified as *Penal Code* (PC) sections 2960-2981 (XC 2974) and enacted into law by the California State Legislature in 1986, sets forth provisions allowing commissioners of the *Board of Parole Hearings* (BPH) to impose mental health treatment by the California Department of State Hospitals (DSH) as a condition of parole for *California Department of Corrections and Rehabilitation* (CDCR) prisoners.[1-22] **The primary intentions of the MDO Act are to protect the public from violent mentally ill offenders and to promote the welfare of these offenders by providing them mental health treatment that reduces their risk of violence related to their illness (thereby reducing their risk of re-offending and being returned to incarceration) and promoting their overall functioning.**

The MDO Act applies only to prisoners in the CDCR system. It presents six specific criteria, all of which must be met for any CDCR prisoner to be certified as an MDO; these criteria appear in MDO section PC 2962. MDO status is determined by forensic psychologists or psychiatrists representing the CDCR and DSH. When these evaluators offer differing opinions, independent forensic mental health evaluators are consulted by the BPH. A prisoner is certified as an MDO by a CDCR chief psychiatrist, and mental health care is provided (involuntarily, in some cases) by DSH as a condition of the prisoner's parole. MDO certification and mental health care are provided at the prerogative of the BPH. Additionally, legal processes are in place that allow a prisoner to contest being certified as an MDO and ensure that prisoners who no longer meet the criteria for MDO status when they receive treatment are decertified and released to the community in a timely manner.

Involuntary Hospitalization and Development of the MDO Act

An issue confronting society, perhaps since the first society was established, is what to do with citizens who represent a threat of harm to others by reason of mental illness. Social responses to this problem have included treatment, confinement with or without treatment, exile, and extermination. Of all of these choices, extermination may seem be the most uncivilized. However, it was practiced at least as recently as during World War II, when the Nazi regime attempted to eradicate individuals who represented a threat of harm to others by reason of mental illness, as well as individuals deemed "incurably" mentally ill. Under the *Aktion T4 Programme*, more than 70,000 people hospitalized in psychiatric facilities in Austria, Germany, and Poland were administered "mercy deaths" between 1939 and 1941. Approximately 23,000 more psychiatric patients were killed under the guidelines of the program between 1941 and 1945.

Among these options, treatment is the most humane. Ideally, the mentally ill individual should be receptive to treatment and the treatment should be provided safely and effectively on an outpatient basis. Some individuals are not receptive to treatment, however, and cannot be treated safely or effectively on an outpatient basis. Involuntary hospitalization may be necessary for their benefit and for the benefit of the general public.

Historically, the parameters for involuntarily hospitalization for mental health treatment have been loosely defined, with few safeguards to ensure that the individual actually requires hospitalization or will be released when the need for involuntary hospitalization ceased to exist. The *Lanterman-Petris-Short* (LPS) Act was enacted into law in 1969 to address these issues.[23] It codified procedures for involuntary psychiatric hospitalization in California. By intent, the provisions of this Act applied to the general citizenry; unintentionally, it created restrictions on the involuntary treatment of chronically mentally ill individuals with past or episodic violent behavior.

Between 1970 and 1985, various political groups tried to codify procedures for the involuntary psychiatric hospitalization of mentally ill individuals who did not meet LPS criteria but had a history of past or episodic violence. This population included prisoners.

Championed by Senator Dan McCorquodale, a legislative act entitled the Mentally Disordered Violent Offender Act was drafted in 1985 that used conviction of a violent felony as proof of a "past history of violence." The word "Violent" was removed from the name of this Act in anticipation of greater community acceptance. It eventually evolved into the *Mentally Disordered Offender Act*.

Efforts to enact MDO legislation accelerated in the aftermath of a violent, near-fatal attack on a popular and talented actress named Theresa Saldana. In 1982, Ms. Saldana was repeatedly stabbed outside her West Hollywood residence by Arthur Jackson, a Scottish national with a psychiatric history extending back to his childhood. Mr. Jackson, who described himself as a "benevolent angel of death" and to his attempt to murder Ms. Saldana as "a divine mission," was convicted of attempted murder and placed under the jurisdiction of the CDCR.

While in prison, Mr. Jackson composed multiple letters to Ms. Saldana in which he threatened to kill her upon his release from prison. In one letter, he wrote that he regretted having stabbed her "because a gun would have given me a better chance of reunion with you in heaven." Ms. Saldana eloquently and effectively brought attention to the fact that there was no legal measure or mechanism to prevent Mr. Jackson from being released from prison to carry out his threats. (In 1996, Mr. Jackson was extradited directly from the custody of the CDCR to the United Kingdom to stand trial for a 1966 robbery and murder. He was found not guilty by reason of diminished capacity and committed to a British psychiatric hospital, where he died in 2004).

Publicity regarding this case evolved into widespread demands for a law that would prevent the release of prisoners like Mr. Jackson, who were known to be mentally ill and violent by reason of their mental illness, directly into the community. With the impetus of public support, the California State legislature enacted the MDO Act on July 1, 1986.

The MDO Act

The MDO Act is codified as California Penal Code sections 2960-2981 (except 2974). Section 2962 sets forth the criteria that must be met for a prisoner to be certified as an MDO. A prisoner must meet all of these criteria to be certified as a MDO. The MDO Act has been amended since its enactment. At that time, it contained five criteria; a sixth criterion addressing *current* dangerousness was added in 1989. In 1999, Criterion Two—which addresses the statutorily defined "qualifying" offense—was expanded to include *implied* threat in 1999. Stakeholders in the MDO process regularly submit proposed amendments to this Act to State legislators.

The MDO Act is a legal statute. Although mental health professionals participated in its development, it addresses mental health issues from a legal perspective, rather than a clinical perspective. The forensic nature of the statute is evident in the precise, specific, legal definitions of terms that are commonly considered clinical terms. The precision and specificity of the definitions seem to effectively eliminate latitude for interpretive variance; however, such variance has been, continues to be, and likely will continue to be put forth.

New Mandates: Development of the CDCR MDO Unit

The MDO Act presented a set of new mandates to the CDCR, including the mandate to identify and evaluate every prisoner who can be certified as an MDO and certify as MDOs those prisoners who meet the statutory parameters. To meet the mandates of the MDO statute of 1986, the CDCR developed and implemented a plan whereby clerical, custody, and mental health staff at individual institutions were assigned the responsibility to identify and evaluate prisoners who are potential MDOs at their institutions. Support was provided by a headquarters-based psychiatrist who was appointed to the newly created position of statewide chief psychiatrist and given the task of certifying prisoners as MDOs. This task was occasionally assigned to institutional psychiatrists, however, who had other professional responsibilities. Assignment of the responsibility of identifying, evaluating, and certifying prisoners as MDO to staff psychologists at individual institutions was logistically feasible through 1994, when prisoners identified as requiring mental health treatment were typically housed in one of only three prisons throughout the state. The viability of this practice was substantially impacted in 1994 by the implementation of the *Mental Health Services Delivery System* (MHSDS), which required decentralization of mental health services. As a result, prisoners requiring mental health treatment were housed in any of the dozens of prisons throughout the state. Revised and refined since its implementation, the MHSDS remains the CDCR model for delivering mental health services to prisoners.

The decentralization of mental health care and dispersion of mentally ill prisoners from three institutions to dozens challenged the ability of the CDCR to meet

its mandates pursuant to the MDO Act. Internal and external audits and analyses revealed that the practice of assigning responsibility for MDO-related tasks to staff at individual institutions (including institutions that had never been charged with MDO-related responsibilities before) was less efficient and effective than desired. They also identified a significant potential for the ethical problem of dual relationships. Some of the prisons now charged with the responsibility of providing mental health services and evaluating prisoners for MDO status had relatively few mental health workers on staff. As a result, the clinician providing mental health services at one of these prisons could be asked to evaluate the same prisoners s/he was treating for their MDO status.

In recognition of the logistical difficulties and potential for ethical shortcomings in this system, the CDCR considered a range of alternatives. A radical and innovative system was proposed by Facility Captain Ron Metz, a peace officer who was familiar with the process of providing mental health care to prisoners as the result of his involvement in the California Men's Colony "Cat X" treatment program. His proposal was to centralize the responsibility for MDO-related tasks. Specifically, Captain Metz proposed the creation of a headquarters-based group of analysts and clinicians who would receive extensive training and ultimately assume responsibility for a MOD evaluation of all appropriate prisoners at every prison in the state. Custody staff at individual institutions would continue to identify prisoners who met MDO referral criteria, but the responsibility for virtually all other aspects of the process would be assumed by the staff of the proposed CDCR MDO Unit.

This proposal was adopted, and the CDCR MDO Unit was activated in 1999. It continues to operate in the manner conceived by Captain Metz and effectively and efficiently ensures that the CDCR meets its mandates pursuant to the MDO statute. The success of the CDCR MDO Unit inspired the development of similar forensic mental health evaluation units within the CDCR and other agencies.

Identifying, Evaluating, and Certifying Prisoners as Mentally Disordered Offenders

Six criteria have been distilled from section PC 2962 of the MDO Act, and all of them must be met for a prisoner to be certified as an MDO. Of these six criteria, one is nonclinical and another is partially clinical. To meet the nonclinical criterion (Criterion Two), the prisoner must currently be serving time for a crime that involved the use or threat of force or violence. This is determined by peace officers, who, unlike most mental health clinicians, have received the training needed to make this determination. To meet the partially clinical criterion (Criterion Five), the prisoner must have received (or must be likely to receive) 90 or more days of mental health care for a *severe mental disorder* (SMD) within the year preceding the date on which his/her release from prison is scheduled (see also Criterion One). The number of days a prisoner has received treatment can be calculated based on information in CDCR databases; these calculations do not involve or require clinical judgment. The determination of whether that treatment was directed toward **ANY** SMD or **THE** SMD (emphases added) referenced in opinions regarding the other statutory criteria does require clinical judgement, however. This determination is made by the MDO evaluator.

Given that these two criteria are entirely or primarily nonclinical in nature and that a prisoner must meet both of them (as well as the remaining four statutory criteria) to be certified as an MDO, nonclinical staff must consider them to determine whether a prisoner requires an MDO evaluation. Prisoners who meet these criteria and for whom a specific release date has been scheduled within approximately one year after the evaluation are referred for such an evaluation. Prisoners who do not meet both of these criteria or do not have a specific release date within approximately one year are not referred for an MDO evaluation. Thus, **a prisoner who perpetrated a violent crime but has never received mental health treatment would not be referred for an MDO evaluation, because that prisoner does not meet all six criteria of the MDO statute.** A prisoner with an extensive psychiatric history who is imprisoned for a crime that did not involve the use

or threat of force or violence would not be referred for an MDO evaluation for the same reason.

When a prisoner meets the MDO referral criteria, the institutional MDO coordinator sends information about that determination to a CDCR MDO unit staff psychologist or regional supervising psychologist. The prisoner is then scheduled for an MDO evaluation by the CDCR MDO unit evaluator.

Until approximately 2001, every prisoner who satisfied the MDO referral criteria was evaluated by an MDO evaluator from both the CDCR and the *Department of Mental Health* (currently DSH). For various reasons, the role of DSH in the evaluation process has evolved, such that MDO evaluations are now initiated by a CDCR MDO unit evaluator, who, based on his/her findings, determines whether an evaluation by a DSH evaluator is warranted. MDO evaluations are generally conducted 2 to 6 months before the date the prisoner is scheduled to be released. The evaluation is usually conducted in prison, although it can be conducted in a county jail (e.g., when the prisoner is out to court as a witness or as a defendant in a pending legal matter), a state hospital (e.g., when the prisoner requires intensive treatment for an acute mental illness), or a community hospital (e.g., when the prisoner is receiving specialized medical treatment).

Evaluation of the Inmate as an Mentally Disordered Offender:

Criterion One

One of the following two decisions is made:

1. **The inmate has a *severe mental disorder* (SMD). (Meets criterion one)**
2. **The inmate does not have an SMD. (Does not meets criterion one)**

To qualify as an MDO, the individual must have an SMD, which is defined by statute in Penal Code 2962(a) as "an illness or disease or condition which substantially impairs the person's thought, perception of reality, emotional process, or judgment, or which grossly impairs behavior, or which demonstrates evidence of an acute brain syndrome for which prompt remission in the absence of treatment is unlikely." Personality disorders, adjustment disorders, epilepsy, developmental disorders, dementia, and addiction to or abuse of intoxicating substances are specifically excluded.[24, 25]

Case Vignette:

Patient A has a history of involuntary psychiatric hospitalizations beginning during adolescence. She was placed in various group homes with a mental health treatment component from age 15 to 18 years. As an adult, she was diagnosed with schizophrenia, paranoid type, while residing in the community and receiving *Supplemental Security Income* (SSI). At the time of her arrest for the qualifying offense, she required hospitalization. She was subsequently determined to be incompetent to stand trial. Throughout her prison term, she has required multiple crisis bed admissions and had to be given medications involuntarily. She has been taking *olanzapine* (Zyprexa) as part of her treatment. During her interview with the examiner, she presented as confused and disorganized and responding to internal stimuli.

Based on this information, Patient A meets requirements for Criterion One.

Criterion Two

To meet the qualifications for Criterion Two, the defendant must have received a determinant sentence pursuant to Section 1170 for one of the following crimes:

- **(A) Voluntary manslaughter.**
- **(B) Mayhem.**
- **(C) Kidnapping in violation of [California Penal Code] Section 207.**
- **(D) Any robbery wherein it was charged and proved that the defendant personally used a deadly or dangerous weapon, as provided in subdivision (b) of Section 12022, in the commission of that robbery.**
- **(E) Carjacking, as defined in subdivision (a) of Section 215, if it is charged and proved that the defendant personally used a deadly or**

dangerous weapon, as provided in subdivision (b) Section 12022, in the commission of the carjacking.

(F) [Certain California sex offenses, including] Rape, as defined in paragraph (2) or (6) of subdivision (a) of Section 261 or paragraph (1) or (4) of subdivision (a) of Section 626.

(G) Sodomy by force, violence, duress, menace or fear of immediate and unlawful bodily injury on the victim or another person.

(H) Oral copulation by force, violence, duress, menace, or fear of immediate and unlawful bodily injury on the victim or another person.

(I) Lewd acts on a child under the age of 14 years in violation of Section 288.

(J) Continuous sexual abuse in violation of Section 288.5.

(K) The offense described in subdivision (a) of Section 289, where the act was accomplished against the victim's will by force, violence, duress, menace, or fear of immediate and unlawful bodily injury on the victim or another person.

(L) Arson in violation of subdivision (a) of Section 451, or arson in violation of any other provision of [Penal Code] section 451 [California arson law] or in violation of Section 455 where the act posed a substantial danger of physical harm to others.

(M) Any felony in which the defendant used a firearm which use was charged and proved as provided in Section 12022.5, 12022.53, or 12022.55 [California's sentencing enhancements for personal use of a firearm].

(N) A violation of Section 12308.

(O) Attempted murder.

(P) A crime not enumerated in subparagraphs (A) to (O), inclusive, in which the prisoner used force or violence, or caused serious bodily injury as defined in paragraph (4) of subdivision (f) of Section 243.

(Q) A crime in which a perpetrator expressly or impliedly threatened another with the use of force or violence likely to produce substantial physical harm in such a manner that a reasonable person would believe and expect that the force or violence would be used. For purposes of this subparagraph, substantial harm shall not require proof that the threatened act was likely to cause great or serious bodily injury.[26-29]

This decision is not subject to clinical review. The case is screened by a peace officer for the presence of force or violence (real, threatened, or implied) then referred for evaluation. Each qualifying crime should appear under Criterion Two. The evaluator summarizes the circumstances of each offense, the details of which are usually obtained from a probation officer report or an arrest report. The inmate's version of each crime and any of the speculative causative factors they present are obtained during a clinical interview.[24]

Case Vignette:

Patient B's legal status summary indicated that he was detained for assault with force likely to produce great bodily injury [PC 245 (a)(4)]. According to a probation officer, Patient B was in a local grocery store, where a store loss prevention officer saw him placing two bottles of alcohol into his coat pockets. The officer approached Patient B as he attempted to leave the store. Patient B struck the loss prevention officer on the left side of his head with one of the bottles. The loss prevention officer fell to the ground, and Patient B exited the business with the two bottles of alcohol. Another member of the grocery store staff followed Patient B into the parking lot, from which Patient B fled with two other subjects. Patient B told the evaluator that on the day of the event he was very unhappy. He had been asked to leave his residence and had nowhere to live. He stated that he went to the store and "attempted to steal alcohol." He said he was stopped by members of the store staff and hit them. He said he then fled, but an hour later decided to turn himself in. He said he had been receiving mental health treatment at the time of the incident. He said he had been taking Buspar, for which he had a prescription,

and claimed that he had been taking it consistently since it was prescribed. He stated that his medication was working well and that he had not experienced any symptoms over the week prior to the incident or on the day of the incident. He said he had not been drinking alcohol or using other drugs at the time. He said he intended to drink alcohol, which is why he stole the bottles.

Based on this information, Patient B meets the qualifications for Criterion Two.

Criterion Three

The SMD was a cause of or an aggravating factor in the commission of the crime for which the individual was sent to prison. This criterion identifies the symptoms of a severe mental illness, as described in Criterion One, as a cause or aggravating factor in a criminal behavior identified in Criterion Two. The SMD does not have to be the predominant cause of the crime or for the inmate to be identified as "legally insane," but it has to be a contributing factor. Therefore, if the severe mental illness contributes in the slightest to the commission of the crime, the prisoner qualifies for an MDO evaluation.[24, 27]

Case Vignette:

Patient C was arrested and convicted of assault with great bodily injury. According to the police report, witnesses observed Patient C in the grocery store talking to someone who was not there. She became angry and started yelling. She then ran up to a man and started hitting him. The man said he never met Patient C before and had not been talking with her. When she was arrested, Patient C said she had been responding to internal stimuli. After a short detention in jail, she was sent to Napa State Hospital, where she was found to be incompetent to stand trial. Her mental health records revealed that her mental health history began during her early teens. She had multiple psychiatric hospitalizations as a child and as an adult. There is a notation in her file that she is not compliant with medication when residing in the community or when she is detained. She recently had to be placed on involuntary psychotropic medications so that her psychiatric symptoms could be stabilized. During an interview with the evaluator, she stated that she would not take medication once she was released and does not believe there is anything wrong with her. There is also a notation in her records that she assaulted the hospital staff several times during the last year and that these assaults were at least in part due to psychotic symptoms she was experiencing at the time.

Based on this information, Patient C meets the qualifications for Criterion Three.

Criterion Four

Criterion Four contains two subsections that address remission: subsection 4A, which examines remission, and subsection 4B, which addresses the ability to be kept in remission.

The MDO Act defines the term "remission" as a finding that overt signs and symptoms of the SMD are controlled by psychotropic medication or psychosocial support. The inmate is not in remission if s/he is simply in a period of waning symptom severity. Per subsection 4A, the symptoms and signs must be in remission as a result of a treatment modality. Because of the recurrent nature of some disorders, a prisoner cannot be considered to be in remission until 6 months of sustained good functioning have been observed.

According to subsection 4B, a person "cannot be kept in remission without treatment" if certain behaviors occurred during the year preceding the case currently being presented before the BPH or before a trial court. This statute also requires the prisoner to be in remission. **Four behaviors are of concern: (a) physical violence, except in self-defense; (b) a serious threat of substantial physical harm upon the person of another so as to cause the target of the threat to reasonably fear for his or her safety or the safety of his or her immediate family; (c) intentional property damage; or (d) not voluntarily following the treatment plan.** The behavior of concern is examined over

the year preceding the anticipated release date. It is also determined whether the prisoner has been following a treatment plan voluntarily. "It is noted that the standard *'shall be whether the person has acted as a reasonable person would in following the treatment plan."* If the inmate had a PC 2602 hearing that resulted in an order for involuntary medication within the qualifying time period, then this matter is considered settled, given that a court of law has already determined that the inmate is refusing medication and that that a refusal of medication is considered unreasonable.[24]

Case Vignette:

Patient D was seen by an evaluator and was observed to be responding to internal stimuli, i.e., the patient was talking to someone who was not in the room and interacting with either people or things that were not in the room. The inmate did so throughout the evaluation. A review of Patient D's mental health records revealed that involuntary psychotropic medications had been prescribed for her and that this order does not expire until 11 months after the date she was seen by the evaluator.

Based on this information, Patient D meets the qualifications set forth in both subsections of Criterion 4. She is not in remission, and she cannot be kept in remission without treatment.

Criterion Five

Criterion Five dictates that the inmate must have been in treatment for an SMD for 90 or more days during the year preceding the date the inmate is scheduled for parole or release.[24, 27]

Case Vignette:

Patient E committed a qualifying offense on 01/01/2017. His prison term began 06/05/2017. He will be paroled on 02/01/2018. According to his mental health records, he started receiving mental health services on 06/10/2017. He has received mental health services since then and received them on the day of the evaluation. Patient E said he intends to continue his mental health care at the parole outpatient clinic (POC) once he is released from prison.

Based on this information, including the fact that he will receive more than 90 days of treatment within the year prior to his release date, Patient E meets the qualifications for Criterion Five.

Criterion Six

Criterion Six dictates that by reason of his or her SMD, the inmate represents a substantial danger of physical harm to others.

Case Vignette:

Patient F has a long-standing mental illness that began in childhood. He also has a long-standing history of noncompliance with medications and has required continuous involuntary treatment with psychotropic medications. Little improvement in his symptoms has been noted in his records. During the current evaluation, he was seen in a crisis bed setting and required restraints and a spit mask to be interviewed. His records indicate that he was placed in a crisis bed setting after attempting to hang himself with a sheet. He was also recently written up in a *Rule Violation Report* (RVR) for assaulting an officer. He told the staff that at that time of the assault, he was responding to internal stimuli (i.e., voices told him to hit the officer). Despite this, he does not think anything is wrong with him and does not feel he needs medication. As the interview continued, he became increasingly disorganized and began to threaten the evaluator and other members of the staff. A review of his records revealed that he has continued to display psychotic symptoms throughout his incarceration and has not been able to work on any parole plans.

Based on this information, Patient F meets qualifications for Criterion Six.

Case Example 1:

Mr. X was convicted of arson of an inhabited dwelling. A police report revealed that at the time of the officers arrival, Mr. X was outside the residence and yelling obscenities while looking up to the sky. When questioned by the officers, he stated that he had been instructed by the devil to burn down the house while his family slept inside. His criminal history began at age 16. His juvenile criminal history includes burglary, battery, and assault. He had been placed in juvenile hall for assault. His adult criminal history includes five convictions for possession of a controlled substance, one conviction for criminal threats, two convictions for theft, and one conviction for arson.

His parents said he suffers from schizoaffective disorder. They said he had been receiving treatment for his illness since he was in his twenties. Mr. X had five psychiatric hospitalizations while residing in the community. He said he usually goes to treatment, but he recently decided that his medications were not working well. So instead, he started using methamphetamine. He said he felt it made him "think better." He said he had been using methamphetamine for about a month before the arson. Mr. X said he realizes now this may not have been a good idea. He said he has not received any treatment for substance abuse/dependence, and he has not attended any Alcoholics Anonymous or Narcotics Anonymous meetings. Mr. X said he does not think he will need to attend any meetings after he is released from prison, adding: "This is not an issue for me anymore." Mr. X has no history of serious physical illnesses, head injuries, or seizures.

During his incarceration, Mr. X required mostly the highest level of mental health care. When he attempted lower levels of care, his psychiatric symptoms appeared to become worse; this included responding to internal stimuli, paranoia, and aggression. Mr. X has been receiving mental health services throughout his incarceration.

Within his last year of incarceration, Mr. X received an RVR for threatening staff. The report revealed that Mr. X told a member of the nursing staff that he knows they have been watching him and he is going to "do something about it." He also said, "I will beat you when no one is looking." There is no mention in the RVR of whether Mr. X's mental illness was a factor in this incident. He said that when he is released from prison, he intends to live with his parents (the same family members who were in the residence that he attempted to burn down). It was noted in his file that his parents do not want him to return to their home. His other parole plans are vague but include applying for SSI, because he was receiving it before because of his mental illness.

During his interview with the evaluator, Mr. X was guarded. He often gave vague answers to questions. He constantly looked around the room. If he felt uncomfortable with the questions, he would become irritable and either raise his voice or give curt answers. At times, he would also glare at the evaluator. He denied experiencing any symptoms, but occasionally appeared to be whispering under his breath. *When the evaluator asked him about it, he became irritated and denied that anything had taken place. His thought process was concrete. His thought content was often about how others were "out to get" him.*

Discussion

Based on this information, Mr. X was determined to have an SMD; thus, he met Criterion One. Having a determinate sentence and a qualifying offense, he also met Criterion Two. It was determined that his mental illness was at least an aggravating factor in the arson incident; thus, he met Criterion Three. He was found to not be in remission at the time of the interview, and he committed another violent offense during the previous year while incarcerated; thus, he met Criterion Four. He required

mental health services throughout his entire incarceration, which well exceeded the 90-day requirement within the year before his parole; thus, he met Criterion Five. Mr. X still required the highest level of mental health care and was not in remission. His records reveal that he performed poorly on parole in the past and that he has a history of impulsive behaviors and acts on command to hallucinations. He also has a history of substance use/abuse/dependence that has yet to be addressed. He has an unrealistic parole plan. By reason of his SMD, Mr. X represents a substantial danger of physical harm to others. Thus, he also met Criterion Six.

Case Example 2:

Ms. Y was convicted of terrorist threats. This is her only offense as an adult, and she has no juvenile criminal history. According to a police report, officers were called to the scene regarding a couple having an argument. Ms. Y had come to her husband's residence to visit their children. She was only supposed to have supervised visits. When her husband said she could not leave with the children, she started yelling at him. She then grabbed a baseball bat that was in the garage and held it above her head and yelled, "If you do not give me the children, I am going to bash your head in and kill you!" Available records note that Ms. Y and her husband were separated because Ms. Y struggles with depression. Her husband told her that he and the children could no longer deal with her mood swings.

Ms. Y said she had been dealing with depression since her mid thirties. *Fluoxetine* (Prozac) had been prescribed for her while she was living in the community. She said she was doing well until her husband decided he wanted to divorce. At that time, her depression worsened. She was hospitalized for suicidal thoughts for about 3 days and then released. She stated that she made one suicide attempt at age 35 by overdosing on her antidepressant.

Ms. Y has been receiving mental health services since her incarceration. She takes her medication consistently and attends all programs. Her mental health records indicate that she had only mild depressive symptoms during the past 4 months. She has never received an RVR. She has no substance use history. She also has no history of head injuries or seizures. Insulin was prescribed for her to control her diabetes.

Ms. Y plans to live with her sister once she is released from prison. She has been offered a job doing clerical work through her church, and she intends to accept it. She does not plan to apply for SSI, and she never received it in the past. She stated she has Kaiser medical insurance and intends to make an appointment with her psychiatrist to take care of her mental health needs and pursue individual therapy to learn more coping skills for her depression. She stated that she takes her medication consistently, but strives to reach a point where she can stop taking medication. She said she would not do so without the agreement of her physician, however, and would want to be monitored closely if and when she ever reaches that point. She said she would also work closely with her parole officer and, if required, attend POC. She stated she is going to attend classes to work toward obtaining visits with her children, over whom her husband currently has sole custody.

Discussion

Based on this information, Ms. Y was found to have an SMD; thus, she met Criterion One. She also had a determinate sentence and a qualifying offense; thus, she met Criterion Two. Her mental illness was not an aggravating factor in the incident; thus, she did not meet Criterion Three. She was not in remission at the time of the interview, given that she still experienced mild depressive symptoms during the 6 months preceding the interview. She had not committed any violent offenses while incarcerated, and she had been cooperative with her entire treatment plan. She met Criterion Four (4A), however, in that she required mental health services throughout her entire incarceration, which well exceeded the 90-day

requirement within the year preceding parole; thus, she met Criterion Five. Although Ms. Y was doing much better, she still had mild depressive symptoms. Her records revealed that she had never been on parole in the past. She does not have a history of impulsive behavior and never had an RVR while incarcerated. Additionally, she does not have a history of substance use/abuse/dependence. She has detailed parole plans. Ms. Y does not represent a substantial danger of physical harm to others by reason of her SMD; thus, she does not meet Criterion Six.

Outcomes

The MDO evaluation process begins (and can end) with an evaluation by a CDCR MDO Unit evaluator that includes a thorough review of the prisoner's central file (institutional record) and Unit Health Record (medical record), as well as a face-to-face interview. If the prisoner does not want to meet with the CDCR MDO Unit evaluator, the evaluator should make every effort to establish contact with the prisoner to arrange for a direct observation of the prisoner's appearance, presentation, and living quarters. The CDCR MDO Unit evaluator may also solicit information from members of the prisoner's treatment team and custody staff who are familiar with the prisoner.

The CDCR MDO Unit evaluator will formulate an opinion of which (if any) of the six criteria the prisoner meets. [NOTE: Determinations regarding Criterion Two are under the purview of peace officers.] The CDCR MDO Unit evaluator will record his or her opinions as soon as possible (i.e., no later than 7 days following the date of the prisoner interview) in a data-sharing platform that can be accessed by the CDCR MDO Coordinator. The CDCR MDO Unit evaluator will upload a completed report of the MDO evaluation to the database as soon as possible (i.e., no later than 14 days following the date of the prisoner interview).

If the CDCR MDO Unit evaluator opines that the prisoner does not have a statutorily defined SMD (see Criterion One) and finds no reason to refer the prisoner for evaluation by a DSH MDO evaluator, the evaluation process is terminated. The prisoner is "cleared for MDO" and released to the community on his/her scheduled release date.

If the CDCR MDO Unit evaluator opines the prisoner has a statutorily defined SMD or otherwise warrants evaluation by a DSH MDO evaluator, the CDCR MDO evaluator will record this information in the data platform. The MDO Coordinator will then arrange for an MDO evaluation of the prisoner by a DSH evaluator.

If both the CDCR MDO Unit evaluator and the DSH MDO evaluator concur that the prisoner meets all of the statutory criteria, documentation—including the reports of the two evaluations—will be provided to a CDCR chief psychiatrist for review. If the CDCR chief psychiatrist concurs with the shared opinions of the CDCR and DSH MDO evaluators, s/he will complete forms certifying his/her opinion that the prisoner is an MDO. Although not common, a CDCR chief psychiatrist might not concur with the opinions of the CDCR and DSH MDO evaluators and choose to not certify the prisoner as an MDO. In such a case, the MDO process can be discontinued and the prisoner can be prepared to be released to the community.

If the evaluator representing one agency (e.g., the CDCR or DSH) opines that the prisoner meets all six statutory criteria but the evaluator from the other agency opines that the prisoner does not meet all six statutory criteria, a situation referred to as a *Difference of Opinion* (DOP) is deemed to exist. In DOP situations, the MDO coordinator refers the prisoner for an MDO evaluation by two MDO evaluators representing the BPH.

If both BPH MDO evaluators opine that the prisoner does not meet all six statutory criteria, the MDO process is discontinued and the prisoner is prepared for release to the community. If one (or both) of the BPH MDO evaluators opine that the prisoner meets all six statutory criteria, the case is presented to a CDCR chief psychiatrist for review and potential certification as an MDO.

If the CDCR chief psychiatrist certifies that the prisoner is an MDO, materials—including reports of all MDO evaluations and the certification documents—will be presented to the BPH commissioners, who will determine whether treatment by DSH should be imposed as a condition of the prisoner's release. Prisoners can contest this condition of parole.

Conclusion

Until recently, it was thought that people with a major mental illness (e.g., schizophrenia, bipolar disorder) were not more likely to commit violent crimes than the general population.[32] In contrast, there is now evidence that a relationship exists between mental illness and violence, especially in persons experiencing a psychosis who do not take their medications.[33-40] Offenders with severe mental illness generally have an acute or chronic mental illness and poor functioning. It appears that a greater proportion of mentally ill persons are arrested compared with the general population. It has been noted that more support is needed for persons with mental illness within the correctional system in general.[30] In 1988, Belcher reported that a combination of severe mental illness, a tendency to decompensate in nonstructured environments, and an inability or unwillingness to follow through with voluntary aftercare and take prescribed medication contribute to involvement with the criminal justice system.[40] With such research noting a link between mental illness and violence, the importance of the MDO Act for those who are incarcerated for violent crimes and are mentally ill becomes apparent. The MDO Act thus has the dual purpose of protecting society from inmates with dangerous but treatable mental disorders and to provide much needed treatment to those inmates.[28]

About the Faculty

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Multiple-Choice Questions

21. The primary purpose(s) of the MDO Act are:

A. To keep inmates incarcerated for longer amounts of time because of the nature of their crime and support the victim.

B. To protect the public from violent, mentally ill offenders and promote the welfare of those offenders by providing them mental health treatment.

C. To ensure that prisoners are receiving mental health services while incarcerated and have housing once they are released from prison.

D. To create more jobs for psychiatrists and psychologists in the forensic field and promote stringent laws against violence.

22. Which criterion is considered to be completely nonclinical?

A. All of the criteria are based on legal issues and considered nonclinical.

B. Criterion One, when the evaluators decide not to use their clinical knowledge for their opinion.

C. Criterion Two, because it addresses the use of threat of force or violence and is determined by peace officers.

D. All of the criteria are considered to be based on clinical expertise, because the evaluations are completed only by psychologists and psychiatrists.

23. The purpose of Criterion Three is to:

A. Prove that the inmate's mental illness was the cause of the qualifying offense beyond a reasonable doubt.

B. Determine whether the inmate's severe mental disorder was a contributing factor in the qualifying offense.

C. Prove the inmate's guilt and intentions to commit the offense.

D. Determine whether the inmate's substance use/abuse/dependence history indicates that s/he now qualifies as having a severe mental disorder.

24. Criterion Six examines:

A. The inmate's risk to re-offend once released from prison if he/she does not have any preplanned housing.

B. Whether the inmate represents a substantial danger of physical harm to others due to his/her severe mental disorder.

C. Whether the inmate is going to re-offend in a nonviolent manner within the first year following his/her release from prison.

D. The inmate's culpability for future crimes and dangerousness once released from the prison environment.

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Best Practices in CME

The Mentally Disordered Offender's Path Within the California Correctional System: California's Mentally Disordered Offender Act

By Juliana Rohrer, PhD; Jeff Kropf, PhD

ID#: L003409

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The Mentally Disordered Offender Act of California allows for the potentially involuntary placement of prisoners in a state hospital for mental health treatment at the time of their scheduled release from prison. This lesson discusses the issue of involuntary psychiatric hospitalization, the genesis of the MDO Act and the *mentally disordered offender* (MDO) Unit of the California Department of State Hospitals, statutory parameters that allow the potentially involuntary hospitalization of prisoners (as set forth by the MDO Act), and the processes of identifying, evaluating, and certifying a prisoner as an MDO.

Key Point 1: Mentally Disordered Offender Act

The Mentally Disordered Offender Act which was drafted in 1985 provides for mandatory mental health commitment as a condition of parole for all prisoners "who have a treatable, severe mental disorder that was one of the causes of, or was an aggravating factor in the commission of, the crime for which they are incarcerated" who are "not in remission or cannot be kept in remission at the time of their parole or upon termination of parole," creating a danger to society.

Key Point 2: Criteria for Mentally Disordered Offender Designation

The individual (1) has a severe mental disorder, (2) the offense the individual was detained for was violent, (3) the mental disorder is not in remission, or cannot be kept in remission without treatment, (4) the mental disorder was a cause of, or an aggravating factor in the commission of the crime for which the individual was sent to prison, (5) the prisoner has been in treatment for a severe mental disorder for 90 days or more within the last year before parole or release date and (6) the prisoner represents a substantial danger of physical harm to others. An individual must meet all six criteria to be placed in a California State hospital under this act.

Key Point 3: Criterion Two

This decision is not subject to clinical review. The case is screened by a peace officer for the presence of force or violence (real, threatened, or implied) then referred for evaluation. Each qualifying crime should appear under Criterion Two. The evaluator summarizes the circumstances of each offense, the details of which are usually obtained from a probation officer report or an arrest report. The inmate's version of each crime and any of the speculative causative factors they present are obtained during a clinical interview.

Key Point 4: Severe Mental Disorder

The term "severe mental disorder" means an illness or disease or condition that substantially impairs the person's thought, perception of reality, emotional process or judgment; or which grossly impairs behavior, or that demonstrates evidence of an acute brain syndrome for which prompt remission, in the absence of treatment, is unlikely. It does not include personality disorders, adjustment disorders, drug addiction, epilepsy, mental retardation, or other developmental disabilities. Penal Code 2962 (a).

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The Role of Long-Acting Injectable Antipsychotics in Schizophrenia

Oliver Freudenreich, MD, FACLP; Sarah A. MacLaurin, PMHNP-BC

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

KEY WORDS: Antipsychotics • Long-acting injectable antipsychotics • Schizophrenia • Relapse • Adherence • Prevention

LEARNING OBJECTIVES: Upon completion of this lesson, clinicians will be able (1) describe to a patient the benefits of a *long-acting injectable* (LAI) antipsychotic over its oral formulation; (2) identify patients who should be prioritized for treatment with an LAI; (3) choose an LAI in collaboration with the patient; and (4) list the limitations of LAIs.

LESSON ABSTRACT: Schizophrenia is for many a relapsing-remitting illness for which a psychotic relapse can be prevented using maintenance antipsychotic treatment. Adherence to antipsychotic therapy is often inadequate, however, which prevents patients from achieving optimal psychosocial gains. This lesson outlines the benefits and choices of LAIs compared with oral antipsychotics to prevent relapse in patients who require antipsychotic maintenance therapy. Being effective in reducing psychotic relapse, LAIs should be considered a first-line treatment option for eligible patients who are likely to discontinue antipsychotics (i.e., first-episode patients and patients at high risk of forensic offenses), although it may be a good choice for any patient who prefers them. LAIs should not be relegated to second-line status (i.e., reserved only for patients who fail oral antipsychotics). Although they are important in the management of schizophrenia, LAIs work best when used as part of a comprehensive treatment plan.

COMPETENCY AREAS: This lesson will expand the clinician's skill set and provide knowledge and skill regarding how to select LAIs and patients who would benefit from their use. It also encompasses systems-based improvement in discussing how to increase utilization of LAIs for eligible patients.

Background

In the majority of cases, schizophrenia is a serious chronic and often life-long condition. Most patients with schizophrenia are not psychotic most of the time while they are in treatment. Instead, they usually experience extensive periods of relative freedom from psychotic symptoms that are interrupted by episodes of psychosis, particularly during times of insufficient adherence to antipsychotics. Thus, the clinical course is similar to that of the relapsing-remitting form of multiple sclerosis. It is unclear whether a relapse is biologically harmful.[1] What is undisputed, however, is that there is a social cost to frequent relapses, which can lead to multiple hospitalizations and accrued "social toxicity" over time. Examples of social toxicity are interrupted schooling, loss of work, loss of friendships, or establishment of a criminal record. At worst, untreated psychosis can lead to accidental death and suicide.[2] It is also undisputed that the ability to manage comorbid medical illnesses hinges on good control of psychiatric symptoms, i.e., psychiatric stability is the basis for good medical care. Thus, a critical aspect of managing schizophrenia is the prevention of psychotic relapses to minimize the amount of time the patient spends being unproductive or incapacitated. Schizophrenia needs to be managed well for the patient to achieve the best possible outcome. If this disorder is poorly managed or not treated at all, the patient will experience ongoing symptoms, poor quality of life, and, possibly, premature morbidity and death.[3]

Antipsychotics are very effective in preventing a relapse to psychosis and its associated social toxicities. A meta-analysis showed a 40% reduction in the risk of relapse at 1 year for patients with schizophrenia who were treated with antipsychotics versus a placebo.[4] This reduction in risk corresponds to a number *needed to treat* (NTT) of 3, which compares very favorably with other highly effective medical treatments. Conversely, discontinuing antipsychotics after they had been used successfully during the first episode of psychosis is associated with a 5-fold risk of relapse.[5] Oral antipsychotics can be prophylactically effective but only when they are taken reliably (i.e., daily) as maintenance treatment. Poor adherence to oral antipsychotics is a major impediment to achieving optimal long-term symptom reduction and achieving psychosocial recovery goals. All too often, care is only provided around acute episodes, with antipsychotic treatment coming to an end immediately after hospital discharge. The result is often readmission to the hospital. The likelihood that a patient with schizophrenia experiencing the first episode of psychosis will still be receiving an antipsychotic after 2 years is only about 50%.[6] Even patients in stable long-term outpatient care often show only partial adherence and fail to achieve a full recovery.[7] Thus, poor adherence to oral antipsychotic therapy is a vexing clinical problem that results in less than optimal symptomatic and functional remission and greatly hinders recovery.

Long-acting injectable antipsychotic (LAI) preparations can be used to avoid some of the problems posed by oral antipsychotics. If dosed correctly, LAIs can reach adequate blood levels over a desired period of time, barring any unusual drug metabolism characteristics. Most importantly, **LAIs provide real-time feedback of actual adherence and make poor adherence visible.** Actual adherence is difficult to measure and requires input from various sources, including self-report, collateral information (e.g., pharmacy records), and therapeutic drug monitoring. There is no gold standard for measuring adherence, and no method or combination of methods is fool-proof. Knowing the actual degree of adherence is critical to avoid mislabeling a patient as "refractory," which can lead to polypharmacy and unnecessarily high doses of medication.

In this lesson, we have provided clinicians facts about the efficacy of LAIs and clinical guidance regarding their use, including patient selection criteria. We emphasize that an LAI is no panacea but is most effective and safe when used as part of a comprehensive treatment plan that includes working with the patient psychotherapeutically and monitoring medical side effects.

Efficacy and Obstacles to Use

The use of a long-acting preparation for long-term management of a chronic condition is superior to the use of an oral preparation that the patient has to remember to take each day. This may seem obvious, but it has been difficult to prove in randomized clinical trials, particularly when the intended outcome is the prevention of relapse or other adverse outcomes associated with nonadherence.[8] The Buckley trial, for example, failed to reveal a difference in relapse rates for patients taking an oral antipsychotic of their choice versus LAI *risperidone* (Risperdal).[9] It is

possible that a randomized controlled trial is not the gold standard for evaluating efficacy because clinical trial volunteers do not reflect real-world patients.[10] Perhaps individuals who sign a consent form and are willing to be assigned to either an oral medication or an LAI are not at high enough risk for poor adherence. Studies based on other trial designs—including mirror image studies (in which each patient serves as his/her own control)—have demonstrated improved efficacy in patients switched from an oral medications to an LAI.[11] Patients in the *Paliperidone Palmitate Research in Demonstrating Effectiveness* (PRIDE) study who were at high risk for forensic complications (e.g., arrests) demonstrated fewer of these complications when they received an LAI before hospital discharge.[12] PRIDE may have been successful because it resembles a real-world scenario in which high-risk patients were enrolled. Several other trials, including randomized trials in first-episode patients, have established that LAIs greatly reduce the risk of relapse over the short term.[13] Over a 12-month period, for example, Subotnik and colleagues[14] found a relapse rate of 5% for LAI risperidone compared with 33% for oral risperidone in 86 patients with schizophrenia during their first psychotic episode.

Effective psychiatric treatment has also been shown to reduce mortality. In a Swedish cohort analysis, mortality decreased by approximately 30% for patients who received an LAI compared with an oral antipsychotic.[15] Furthermore, the regularly scheduled visits required for injections can provide an opportunity for other interventions, such as smoking cessation or illness management recovery, which might contribute to the survival benefit seen in LAI-treated cohorts.

Despite clear evidence of equal or improved efficacy with an LAI, these drugs remain underused in the United States. Their low rate of use (approximately 10% to 15%) is not consistent with the high rate of nonadherence in schizophrenia.[16] LAI use varies greatly with geography, ethnic factors, and other issues, which suggests that the reason for selecting an LAI is much more complex than merely to prevent nonadherence. Important obstacles include inadequate insurance coverage or access to care, patient and clinician preference, and confidence in the use of this formulation.[17] As of 2014, seven states had classified the LAI as a medical benefit rather than a pharmacy benefit, which places the administrative burden on the provider and makes the medication less accessible to the patient. Health insurance coverage also affects the personnel who are permitted to administer medications. Recent changes in insurance coverage rules in New York State have determined that a licensed practical nurse (LPN is the most cost-effective clinic staff person to administer LAIs.[18] Unfortunately, LPNs are not always available in many outpatient psychiatric settings. Another obstacle to the administration of LAIs is the attitude of the clinician toward their use.[19] If the clinician perceives LAIs as a coercive form of treatment, s/he might subtly convey this attitude to the patient or not offer them as a routine choice. Indeed, LAIs are often presented as the treatment of last resort (i.e., when coercion is believed to be necessary). If LAIs are described as being less intrusive to everyday life with clear benefits for survival, however, some patients might prefer one over an oral medication.

The physician's attitude toward coercion may be at least partially influenced by cultural attitudes. In countries with a strong libertarian tradition and emphasis on patient autonomy (e.g., the United States), physicians might err on the side of the least assertive treatment, particularly if side effects are a concern. In a shared decision-making paradigm, however, the clinician must present the treatment options (including LAIs) in a way that does not convey a lack of trust in the patient's ability to make the best choice for his/her circumstances.

Patient Selection

An LAI may be the best choice for patients who require maintenance treatment with an antipsychotic (exceptions are identified in the following section). **As part of the shared decision-making process for selecting a treatment option, an LAI should be offered routinely as a first-line choice versus oral medications to all patients with schizophrenia**. For example, *lithium* (Lithobid, Lithate), may remain the mainstay of maintenance treatment for patients with bipolar disorder, but second-generation antipsychotics are being selected with increasing frequency. Similarly, an LAI could be offered as an effective choice to prevent relapse.[20]

The potentially life-saving effect of LAIs should be discussed with patients at high risk for poor adherence, particularly if relapse exacts a high price. **Patients who have the most to gain from an LAI include first-episode patients and patients with a history of criminal justice involvement who are at high risk of re-offending.** First-episode patients who do not have long-term

experience with their illness are at very high risk of drug discontinuation and a subsequent relapse. Relapse rates of more than 90% are seen after 2 years.[21] LAIs remove the need to focus on issues involved in ensuring that an oral medication is taken reliably, which can involve a considerable amount of nagging. They may benefit those patients who have been involved with the criminal justice system, and who are particularly at risk for re-offending due to impulsive, aggressive action during periods of acute psychosis, thus accruing additional convictions, which makes reintegration into society all but impossible.

Patients with chronic illnesses might also benefit from switching to an LAI, even if their adherence to an oral agent appears to be sufficient. Both clinicians and patients tend to overestimate adherence;[22] as a result, the oral treatment regimen can become unnecessarily complex and involve increasingly high doses to compensate for symptoms arising as a result of unrecognized partial adherence. On the other hand, stable patients on an older antipsychotic might not benefit from a switch to a newer antipsychotic (which is often done to reduce the risk for tardive dyskinesia), and a subgroup of patients may be unable to switch successfully and might decompensate during the switch and show new side effects.[23]

Some patients being treated with *clozapine* (Clozaril, FazaClo) may benefit from the addition of an LAI to their treatment regimen. Patients taking clozapine may be at increased risk for poor adherence because of poor insight or disorganization. These patients may benefit from the addition of LAI *aripiprazole* (Abilify, Aristada) to their therapeutic regimen to achieve both metabolic and psychopathological benefits.[24] In particular, they may benefit from the assurance of therapeutic coverage if they forget a dose or two of clozapine or the prevention of a serious relapse if clozapine therapy is discontinued.

Patients are at a particularly high risk of harm when they are discharged from an acute setting after receiving an injection and no follow-up is provided or a gap in follow-up (e.g., due to insurance issues) is very likely. An LAI can be administered around times of care transition (e.g., discharge from inpatient to outpatient care or discharge from an emergency room). Even if follow-up is unlikely, one injection before discharge can provide at least some period of stability and allow a gradual decline in serum drug levels, thereby reducing the risk of a sudden relapse on discontinuation of the drug.

LAIs can also be beneficial in difficult-to-engage patient populations. A visiting nurse or member of a *Program of Assertive Community Treatment* (PACT) team can administer an LAI in a community setting if the patient cannot get to the clinic. Thus, when combined with psychosocial treatment, an LAI can be effective in populations that are traditionally very difficult to treat, such as homeless patients with serious mental illnesses and poor adherence.[25] An LAI can also be an important component of court-ordered, *assisted outpatient treatment* (AOT) when coerced care is needed to help the patient reside safely in the community.[26] In states in which AOT is available, LAIs would allow patients with very limited engagement with the healthcare system to receive court-ordered treatment.

Table 1 provides a summary of patients who should be selected for LAIs.

Table 1:
Patient Selection for LAIs

- Any patient who prefers an LAI over oral antipsychotics
- Important to prioritize:
  - First-episode psychosis
  - Forensic history associated with prior relapse
- Harm reduction approach:
  - Injections at time of care transitions
- Not appropriate for LAI:
  - History of NMS*
  - Sensitivity to extrapyramidal symptoms that require less tight D2 binding
  - Refractory patients (LAIs are not a substitute for clozapine)

**Neuroleptic malignant syndrome.*

Contraindications and Cautions:

Several patients groups should *not* receive LAIs. **Many clinicians consider a history of *neuroleptic malignant syndrome* (NMS) to be a contraindication for the use of LAIs.** Patients with epilepsy should only receive an LAI after a trial of the oral formulation to ensure that any reduction in seizure threshold associated with the antipsychotic does not worsen seizure control.

Patients who are treatment-refractory are not good candidates for an LAI. Such patients should begin with clozapine instead. A brief trial of an LAI may be a good

intermediate step to ensure that their lack of response is neurobiologically based (i.e., true refractoriness) and not an indication or poor adherence or an unusual drug metabolism (i.e., pseudorefractoriness).

In principle, antipsychotic-naïve, first-episode patients are good candidates for LAIs for stabilization and during the maintenance phase of treatment. They should, however, receive an oral antipsychotic first to determine drug tolerability, i.e., to rule out allergic reactions and sensitivity to extrapyramidal side effects. An allergy to the oral medication will preclude the use of an LAI. In some cases, an allergy to the vehicle can be problematic.

LAI Drug Selection

The decision to prescribe an LAI is guided largely by the desired injection frequency and predicted side effects (Table 2). Clinicians can chose between older first-, and newer second-, and third-generation antipsychotics (the partial agonist, aripiprazole). As indicated by the results of the CATIE trial, in which older and newer antipsychotics were found to be equally effective,[27] **the difference between older and newer LAIs lies in their side effect profile and not in their efficacy**. McEvoy and colleagues[28] conducted a trial comparing the efficacy and safety of an older reference LAI (*haloperidol decanoate* [Haldol injection]) with a newer LAI (*paliperidone palmitate* [Invega, Invega Trinza]). They found similar rates of efficacy failure (mostly in the form of a psychiatric hospitalization) and clinical efficacy but different side effect profiles, which were consistent with the known side effects for each medication. In some settings, administrative issues, including cost or specific injection requirements (olanzapine [Zyprexa]; see below), will limit the choice of LAI. Additional considerations include the need for oral overlap or the availability of a loading-dose strategy to achieve therapeutic blood levels more quickly than standard monthly dosing. In inpatient settings where the duration of stay is measured in days, LAIs can be employed in lieu of oral pills where loading is possible, as blood levels can become therapeutic within a few days.

Table 2:
Long-acting injectable Antipsychotics (LAIs)

Drug	Dose strengths	Dose (IM) & Frequency	Notes
Haloperidol decanoate [HALDOL DECANOATE]	Vials 50mg/ml Vials 100mg/ml	50 - 200 mg monthly Other dose intervals are possible	Initiation: overlap with oral antipsychotic Loading dose strategy possible Maintenance dose equals 20 x oral dose
Fluphenazine decanoate [PROLIXIN DECANOATE]	Vials 25mg/ml	6.25 - 25 mg every 2 weeks Other dose intervals are possible	Initiation: overlap with oral antipsychotic
Risperidone microspheres [RISPERDAL CONSTA]	12.5mg, 25 mg, 37.5 mg, 50 mg	12.5-50 mg every 2 weeks	Initiation: 3 week overlap with oral antipsychotic Main release of drug occurs 3 weeks after injection 50 mg every two weeks corresponds to 4 mg/d oral (50 mg is highest IM dose)
Paliperidone palmitate [INVEGA SUSTENNA]	39 mg, 78 mg, 117 mg, 156 mg, 234 mg	39-234 mg monthly	Loading dose of 234 mg [deltoid!] to initiate (no oral overlap needed), 2nd dose one week later, the monthly 156 mg monthly corresponds to 9 mg/d oral
[INVEGA TRINZA]	273 mg, 410 mg, 546 mg, 819 mg	273-819 mg every 3 months	Every 3 months dose can be used after 4 months of monthly injections 546 mg corresponds to 9 mg/d oral
Olanzapine pamoate [ZYPREXA RELVPEVV]	150 mg, 210 mg, 300 mg, 405 mg	150 or 300 mg every 2 weeks 405 mg monthly	No overlap with oral antipsychotic (higher initiation doses) Monitor for 3 hours of observation for post-injection delirium/sedation syndrome (PDSS)* 300 mg monthly corresponds to 10 mg/d oral
Aripiprazole monohydrate [ABILIFY MAINTENA]	Vials 200 mg/ml	160mg- 400mg monthly	Initiation: 2 week overlap with oral antipsychotic 300 mg corresponds to 10 mg/d oral; 400 mg to 15 mg/d
Aripiprazole lauroxil [ARISTADA]	441 mg, 662 mg, 882 mg, 1064 mg	441,662,882 mg every 4 weeks 882 mg every 6 weeks 1064 mg every 2 months	Initiation: 3 week overlap with oral antipsychotic AL_{NCD} for initiation under FDA review Inject rapidly due to non-Newtonian fluid characteristics Only lowest dose of 441 mg dose can be given in deltoid 441 mg monthly corresponds to 10 mg/d oral 662 mg monthly or 1064 mg every two months corresponds to 15 mg/d oral 882 mg monthly corresponds to 20 mg/d oral (highest IM dose)

An oral test dose is required for all antipsychotic agents if the patient has never been exposed to an intramuscular antipsychotic.
AL_{NCD}, Aripiprazole Lauroxil NanoCrystal Dispersion.
*See REMS website for olanzapine pamoate31

The side effects of an LAI are the same as those seen with its oral equivalent.[29] LAIs do not carry a higher side-effect burden, except for the additional side effects related to the injection itself, which range from redness to the formation of abscesses (rare) at the injection site. If more side effects are observed with an LAI (e.g., extrapyramidal symptoms, weight gain), it is very likely that adherence to the oral formulation was subpar.

An injection-related complication unique to olanzapine is the onset of severe sedation, confusion, slurred speech, or coma within a few minutes to a few hours after the injection (median time from injection to symptoms: 25 minutes). This is seen when olanzapine is inadvertently injected directly into the bloodstream.[30] The symptoms will vary with the extent of the olanzapine overdose. The risk of this *post-injection delirium/sedation syndrome* (PDSS) prevents patients from receiving LAI olanzapine in many settings unless they are prepared to comply with certain FDA *Risk Evaluation and Management Strategy* (REMS) requirements (including a 3-hour post-injection observation and having ready access to emergency response services), which are designed to manage this complication.[31] PDSS is a rare side effect, occurring in less than 0.1% of injections, or about once in every 1400 injections. Most patients recover quickly within hours or up to 3 days at the most. A good injection technique is critical to prevent this complication.

It is unclear whether a steadier plasma level offers any clinical benefit or even fewer side effects. One caveat about oral versus LAI conversion factors is that they are not necessarily 1:1 over a specific period of time. Enough clinical experience with LAIs exists, however, to suggest approximate dose equivalents between the oral and long-acting preparations. These appear in Table 2.

Practical Management Issues

Convincing patients to use an LAI requires a willingness to prescribe LAIs and also to have some basic negotiating skills.[32] If shared decision making is taken seriously, LAIs should be discussed with every eligible patient, with the discussion based on evidence for their efficacy. Even if no personnel are available to administer LAI injections, creative solutions can be pursued (e.g., working with a primary care office). As described earlier, olanzapine pamoate is a special case that requires post-injection monitoring, which not all clinics can provide.

The transition to an LAI often requires a period of overlap with an oral antipsychotic (see Table 2). A smaller decanoate dose should be considered to ensure tolerability of the oily vehicle. Patients should never be injected with a medication to which they have not been previously exposed. **An oral tolerability trial is always necessary before administering an LAI the first time, because patients who have never received an antipsychotic are usually very sensitive to its side effects.**

A major clinical decision will involve the frequency of injection. Longer injection intervals carry several advantages (e.g., more flexibility for patients) and disadvantages (e.g., risk of disengagement from care, missed therapeutic encounters). Dose adjustments must be made based on pharmacokinetics, clinical response, and side effects. *Therapeutic drug monitoring* (TDM), which involves monitoring of antipsychotic levels in the blood, is available for all antipsychotics that are available as LAIs and can be integrated into routine care to achieve personalized dosing.[33] Population-based blood level norms for a given steady-state dose have been established through clinical trials. These norms are applicable even when the relationship between blood level and response (the "therapeutic window") is less well established. TDM can help clinicians understand any unexpected lack of efficacy or breakthrough symptoms toward the end of the injection interval, including the appearance of withdrawal dyskinesias. Clinical trials have also been used to evaluate dose ranges for older antipsychotics. It is known that higher doses confer no advantage over neuroleptic threshold doses for these agents[34] and that conversely, a dose can be too low. Kane and colleagues[35] randomized patients to monthly injections of 25 mg, 50 mg, 100 mg, and 200 mg of haloperidol decanoate. The lowest dose resulted in a relapse rate of 60% compared with rates of only 15% to 25% for the three higher doses. There were no differences in extrapyramidal side effects for the three higher doses. *Patient Outcomes Research Team* (PORT) dosing guidelines for schizophrenia, combined with TDM, can be used to optimize the dosing of older antipsychotics and avoid unduly high or low doses.[36] For second-generation antipsychotics, minimally effective doses that avoid underdosing have been proposed based on clinical trial results.[37]

Nurses typically assume responsibility for administering injections and managing injection site reactions. With recent advancements in LAI options, an increasing number of skills has become necessary administer these injections. Older decanoate antipsychotics (haloperidol

and *fluphenazine decanoate* [Prolixin, Modecate]) are oil-based and, thus, require a slow delivery rate, which can make their administration painful. Decanoates can be administered using flexible dosing, however, and dosing can be adjusted at the time of injection. Prescribers and nurses need to attend carefully to the concentration of haloperidol in particular, because it comes in both 50-mg/mL and 100-mg/mL concentration which can easily be mixed up in a busy clinic. By contrast, second-generation antipsychotics are available in aqueous solutions, several in prefilled syringes that allow ease of administration at the expense of flexibility. Aripiprazole lauroxil must be injected very rapidly because of its unique fluid characteristics. The drug should not be aspirated before injection to avoid clogging. Because LAIs are injected intramuscularly, patient muscle characteristics (e.g., muscle mass) must be considered, along with specific instructions from the manufacturer, when deciding where an injection is to be made and the length of the needle that should be used. Deltoid injections are specified for loading doses of LAI paliperidone because of the higher blood perfusion rate in this muscle. Deltoid sites are prohibited for aripiprazole lauroxil injections larger than 441 mg because of the particle size and distribution pattern of the medication. Injection site reactions can range from mild pain to the formation of nodules and abscesses. Site reactions occur less often than expected, however, and are usually limited to pain. Good injection techniques and appropriate site selection (i.e., with sufficient muscle mass) are critical to minimize injection pain. Local reactions can be reduced by using low-volume, high-concentration preparations. Good injection techniques required to reduce injection-related complications are summarized in Table 3.

Table 3:
Principles of Good Injection Technique

Documentation	Drug, Dose and Volume, Date, Injection Site, Clinician
Supplies	Gloves, gauze, alcohol swabs, Band-Aid Syringes (3-5 ml syringes) Needles (21-gauge 1″ and 1.5″ (and 2″) for deconoates* SGA LAIs come in kits with necessary syringes and needles
Site selection	Dependent on: - body habitus and injection volume - loading or maintenance dose# - last site used - manufacturer instructions Site rotation highly recommended to minimize complication
Technique	Z-track: Specific technique that displaces outer layers of tissue to secure medication within the muscle, thereby reducing leakage to subcutaneous tissue and minimizing skin lesions and pain - Position the patient so that the muscle at the injection site relaxes. - Clean the site with an alcohol pad and let it thoroughly dry. - Displace tissue by pulling skin laterally or downward with the non-dominant hand - Inject firmly, rapidly at a 90-degree angle† - Aspirate to ensure medication does not enter a blood vessel - Inject slowly at a rate of 10 seconds/mL - Wait 10 seconds before withdrawing the needle - After withdrawing the needle release the skin to its starting position. - Use dry gauze to apply very gentle pressure to the puncture site
Post-Injection Management	Patients are instructed to resume normal activity immediately, keeping the injection site clean. *If muscle discomfort develops:* apply warm heat, take over the counter oral pain medication, and have patient call the clinic if pain persists past 72 h *If nodules develop:* have patient medically evaluated; utilize other sites for as long as possible *If there is ongoing redness, swelling, discharge from injection site:* have patient medically evaluated Olanzapine pamoate requires a 3 h observation for signs and symptoms of post-injection delirium/sedation syndrome

*Length depends on the size/build of the patient.
#Loading doses of paliperidone palmitate should be administered in the deltoid for more rapid distribution.
†Aripiprazole lauroxil specifically requires no aspiration and rapid injection of syringe contents.

LAIs are only therapeutic tools and work best when they are part of a comprehensive care plan that includes side-effect monitoring (e.g., for metabolic syndrome and tardive dyskinesia). The use of LAIs provides regular opportunities for therapy and health maintenance, as well as for counseling (e.g., for smoking cessation). A clinic that offers LAI administration can set up an injection sub-clinic, applying the principles of population-based management. The use of such clinics can be monitored using a spreadsheet to keep track of all of the patients receiving an LAI. Arranging care around such a sub-clinic may allow for better tracking of missed visits or missed metabolic monitoring. Guideline-concordant side effect monitoring, with particular attention paid to metabolic monitoring and regular tardive dyskinesia screening, is critical to prescribe LAIs safely. Up-to-date and user-friendly guidelines are provided by the British *National Institute for Health and Care Excellence* (NICE) service[38] (see Table 4).

Table 4:
Medical Monitoring of LAIs

Before starting treatment (baseline assessment), obtain the following information about the patient:
- Weight
- Waist circumference
- Pulse and blood pressure
- Fasting blood glucose, glycosylated hemoglobin (Hb_{a1c}), blood lipid profile, and prolactin levels
- Assessment of any abnormal movement
- Assessment of nutritional status, diet, and level of physical activity
- Consider ECG, particularly if cardiovascular risk factors are present

During treatment, monitor the following:
- Emergence of movement disorders, particularly tardive dyskinesia
- Weight—weekly for the first 6 weeks, then at 12 weeks, at 1 year, and then annually
- Waist circumference annually
- Pulse and blood pressure at 12 weeks, at 1 year, and then annually

Note: Consider creating a spreadsheet to track results over time

Based on: National Institute for Health and Care Excellence (NICE) Guidance: Psychosis and schizophrenia in adults: prevention and management. 2014. Available at: https://www.nice.org.uk/guidance/cg178.

Limitations of LAIs

LAI preparations are not available for all oral antipsychotics. Patients who are exquisitely sensitive to extrapyramidal side effects might not be able to tolerate any LAIs (which all bind tightly with dopamine receptors), even if they are dosed carefully. Patients who are very sensitive to extrapyramidal side effects and can only tolerate a weakly dopamine-binding antipsychotic like quetiapine may not be good candidates for LAI therapy. Similarly, no long-acting form of clozapine is available for refractory patients.

An LAI can only work if the patient agrees to take it—unless the drug is given within the framework of coerced care. Merely prescribing an LAI will not turn an unwilling patient in a willing one. Poor clinical decisions are often made around periods of care transition, resulting in unrealistic and chaotic treatment plans. For example, all too often the decision to "convince" a patient to accept an LAI is left to the outpatient team, and the patient is discharged from an inpatient unit (where he was admitted because of poor adherence) with a prescription for oral medications. Patients might also push for an LAI with a long injection interval so they can "be left alone." If there isn't a good working alliance to begin with, infrequent visits will be an obstacle to improving clinical outcomes. A visiting nurse may be an alternative for patients with inadequate engagement with a clinic. The use of a visiting nurse service may carry several risks, however, in that it may limit the ability to find out about missed injections and provide additional therapeutic interventions on a timely basis. This can be accomplished, with good communication among the involved services. For some patients, the more frequent and regular clinic visits required to receive injections can provide structure and a routine that may have a stabilizing influence on the overall clinical course.[39] Some clinical trials that failed to show superior efficacy for LAIs probably provided good solid clinical care with frequent visits and follow-up for all patients, which may outweigh any differential efficacy that LAIs might have in routine settings.

Having a patient on a long-acting antipsychotic might lead to clinician complacency and less input in the decision-making process is asked from the patient. By relegating this aspect of their autonomy, patients who accept LAI therapy might pay a psychological price. Vigilance is

required to encourage appropriate self-management and not allow a paternalistic relationship to develop between the clinician and the patient.

Even if taken regularly, the LAI is no panacea. It cannot be emphasized enough that LAIs do not constitute comprehensive treatment of schizophrenia.[40] There is a risk of losing sight of the fact that LAIs merely comprise a tool and not a therapeutic end in itself. Particularly in resource-poor settings, getting patients their injection can become the sole purpose of such treatment, and the tools can be confused with the goals of treatment. Merely giving injections without medical monitoring is also unsafe medical practice. Finally, LAI maintenance treatment does not provide 100% protection against a relapse—only a reduction in relapse risk.

Summary and Conclusions

LAI antipsychotics comprise a logical clinical choice for the long-term management of a relapsing-remitting illness like schizophrenia where the prevention of relapse is critical to achieve the treatment goal of symptomatic and functional remission. Psychiatric stability serves as the foundation for psychiatric rehabilitation, self-management of medical disorders, and psychological recovery.

While the efficacy of oral antipsychotics and LAIs is the same in research settings, the effectiveness of LAIs in routine settings appears to be superior, given that adherence is better in such settings and nonadherence can be more easily recognized and addressed in a timely fashion.

A wide selection of LAIs for a variety of clinical situations is now available that includes first-, second-, and third-generation antipsychotics (the partial dopamine agonist, aripiprazole) for a choice based on side effects. Flexible dosing allows for injections as infrequently as every 3 months; even longer-acting preparations are currently under development.

It behooves clinicians to include LAIs in their discussion of first-line treatment options rather than as a choice of last resort. Patients at high risk for antipsychotic discontinuation whose life may fall apart if they experience a relapse should be specifically selected for this treatment (e.g., first-episode patients, patients with forensic histories).

About the Faculty

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L003410

Multiple-Choice Questions

25. What is the main rationale for using LAIs over oral antipsychotics?

A. They reduce the need for overall clinical care.

B. They offer better efficacy than oral medications.

C. They have fewer side effects.

D. Poor adherence is easily recognized.

26. Which patients should be offered LAIs as a first-line treatment?

A. First-episode patients.

B. Nursing home patients.

C. Emergency room patients.

D. Group home patients.

27. Which factor is *not* critical in selecting an LAI?

A. The injection interval.

B. The side effect profile.

C. The efficacy of newer LAIs compared to older decanoate LAIs.

D. The possibility of monitoring post-injection for LAI olanzapine.

28. Which patient should *not* receive a long-acting antipsychotic?

A. Patient with a history of *neuroleptic malignant syndrome* (NMS).

B. Patient with a history of seizures.

C. Patient with a blood clotting disorder.

D. Patient with cardiovascular disease.

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Best Practices in CME

The Role of Long-Acting Injectable Antipsychotics in Schizophrenia

By Oliver Freudenreich, MD, FACLP; Sarah MacLaurin, PMHNP-BC

ID#: L003410

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

For many patients, schizophrenia is a relapsing-remitting illness for which a psychotic relapse can be prevented using maintenance antipsychotic treatment. This lesson outlines the benefits and choices of *long-acting injectable antipsychotics* (LAIs) compared with oral antipsychotics for relapse prevention. LAIs should not be relegated to second-line status (i.e., reserved only for patients who fail oral antipsychotics) but offered routinely to all patients as a good treatment option. LAIs should be prioritized for eligible patients who are very likely to discontinue antipsychotics (first-episode patients) or for whom relapse is costly (patients at high risk of forensic offenses when psychotic). LAIs work best when used as part of a comprehensive treatment plan that includes guideline-concordant side effect monitoring.

Key Point 1: Rationale for LAIs

Schizophrenia as a remitting-relapsing psychotic illness that requires maintenance therapy with antipsychotics to reduce complications due to psychotic relapse such as suicide, violence, loss of a job, or loss of social networks.

Key Point 2: Patient Selection for LAI

LAIs should be offered routinely, not as a last resort, to first-episode patients; patients at high risk of committing a criminal offense; or any patient who prefers them over oral treatment.

Key Point 3: Selection of LAI

The LAI choice is guided by side-effect profile and injection frequency. All available LAIs are about equally effective, with no difference between first- and second-generation antipsychotics.

Key Point 4: Safe Use of LAI

LAI therapy does not constitute comprehensive treatment of schizophrenia but requires a systems-based approach that should include monitoring of side effects (e.g., metabolic syndrome and tardive dyskinesia).

Notes

L003411

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Competing With Learned Fear: Implications of Fear Extinction for Clinical Intervention

Leah Weingast; Haley E. Haas; Seth Davin Norrholm, PhD

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

KEY WORDS: Posttraumatic Stress Disorder • Fear Extinction • Psychophysiology

LEARNING OBJECTIVES: On completing this lesson, clinicians will be able to (1) identify the signs and symptoms of *posttraumatic stress disorder* (PTSD); (2) delineate the fear-learning mechanisms underlying trauma-, stressor-, and anxiety-related disorders; (3) explain the paradigms used to identify clinically relevant fear-learning impairments and the neurobiological mechanisms underlying these impairments; and (4) describe predominant PTSD treatment practices and trends in translational and clinical research into fear learning and PTSD.

LESSON ABSTRACT: A comprehensive review of clinical models of PTSD and fear conditioning is presented. The predictive clinical value of objective psychophysiological measures of fear learning is highlighted. These measures are used to operationalize the learning and memory processes underlying healthy and pathological fear learning. One measured feature is the fear-potentiated startle, which can be used to study the extinction of learned fear in both preclinical animal studies and human clinical applications. Fear-related symptoms of PTSD can be conceptualized as failure to inhibit fear and further explored through fear-learning profiles. Heterogeneity of fear learning in human and animal models may represent intermediate phenotypes and biomarkers that moderate and mediate fear learning and PTSD symptomatology in previously traumatized individuals.

COMPETENCY STATEMENT: Clinicians will gain knowledge of measures that can be used to operationalize the learning and memory processes underlying healthy and pathological fear learning. By examining the clinical models of PTSD and risk factors that may prohibit one to extinguish fear memories, clinicians can help improve treatment outcomes in patients by tailoring psychological and pharmacological treatments.

Introduction

Posttraumatic stress disorder (PTSD) is a heterogeneous mental illness that can arise after exposure to a traumatic event. PTSD can develop in multiple populations and, thus, presents a significant public health issue.[1] Trauma exposure can occur through direct exposure to an event, by witnessing an event, or by learning about an event affecting a relative or close friend. It can also develop through indirect exposure, e.g., exposure to the aversive details of a trauma characterized by death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence.[2] Based on criteria presented in the *Diagnostic and Statistical Manual of Mental Health, 5th Edition* (*DSM-5),* the national rate of trauma exposure has been estimated to be as high as 89.7%. Only a fraction of the US population has presented with PTSD, however.[1] Clearly, there is a discrepancy in the role of resilience in the development of posttraumatic sequelae in some populations compared with others. To examine the factors that mediate this discrepancy, fear-related signs and symptoms of PTSD should be conceptualized and modeled in laboratory settings as failure to extinguish an elevated physiological threat response following a signal of danger or harm.[3, 4] Differences in the ability to extinguish threat responses have been highlighted in both rodent models and in humans as predictors of posttraumatic symptom development or resilience.[3, 5-7]

PTSD Symptom Criteria (Adapted from the DSM-5[2])

(1) Distressing re-experiencing, such as flashbacks where a person feels as though s/he is being exposed to elements of the traumatic event again

(2) Avoidance, including averting thoughts and feelings related to the trauma

(3) Negative alterations in cognition and mood, such as detachment from others and a loss of interest in activities

(4) Hyperarousal symptoms manifested by sleep disturbances and extreme alertness.[2]

Key Concept: *Intermediate phenotype*—a trait that represents fundamental neurobiological mechanisms related to the etiology of the clinical presentation of an illness.[7]

Key Concept: *Biomarker*—a measurable indicator of a healthy or pathological biological process. It may be used to identify vulnerability to a disorder as well as to preventive interventions. For example, biomarkers have been used to link fear learning deficits with PTSD symptoms.[8, 9]

Translational and Clinical Research in Traumatized Populations

A significant body of literature has been developed based on the implementation of psychophysiological paradigms used to test preclinical and clinical models of PTSD and to assess treatment outcomes.[8, 9] These paradigms are based on Pavlovian threat conditioning, or fear conditioning, which allows the use of quantitative objective measures to identify and differentiate components of PTSD, most notably those related to the dysregulation of fear processing.[9, 10] Fear conditioning, which has its foundations in Pavlovian classical conditioning, is a form of associative learning in which a neutral stimulus is paired with an *unconditioned stimulus* (US) that naturally evokes a defensive *unconditioned physiological response* (UCR). The stimulus, which previously was neutral, becomes a *conditioned stimulus* (CS) through its association with the US and elicits a defensive conditioned response in the absence of the US. The association of US and CS results in the consolidation of a fear memory that can be readily expressed until the learning parameters are changed. One such change occurs when the CS is later presented repeatedly without the US; this may establish a more dominant memory trace than that of the original CS-US association. This new memory trace develops through the process of fear extinction. If successful, the new extinction memory will dominate over the original fear memory, even after the fear memory has been consolidated.[10] Characteristics of fear extinction in an individual, such as the amount of conditioned fear expressed during early extinction (i.e., fear load), have

been pinpointed as intermediate phenotypes underlying fear-related psychopathologies.[6] Psychophysiological data derived from fear conditioning and extinction paradigms utilized by Norrholm and colleagues have suggested that fear load has implications for interventions in exposure therapy, given that it has predicted a significant number of intrusive symptoms and can be accessed through fear inhibition and extinction.[6] The primary objective outcome used by these researchers is the fear-potentiated startle, i.e., the relative increase in frequency or magnitude of the acoustic startle response in the presence of a CS that has been repeatedly paired with a US. The fear-potentiated startle is an ideal translational paradigm for studying the neurobiology of fear in rodent models and in humans because of the high level of consistency in methodologies across mammalian species. Furthermore, a fear-potentiated startle method can be used to investigate deficits in the ability to suppress exaggerated fear responses, providing highly clinically relevant information for evaluating fear-related disorders such as PTSD.[11, 12]

Redefining PTSD

PTSD was added to the DSM-IV as a standalone mental disorder in 1980 after long being described phenomenologically in clinical terms without formal recognition. Dollard and Miller developed a two-factor theory before PTSD was recognized as a distinct mental disorder, positing the acquisition of fear as a result of classical conditioning, a concept that is still used in psychotherapeutic and research approaches to this disorder.[13, 14] The DSM-5 incorporated several committee-designated changes to PTSD criteria in 2013, including modification of the A1 stressor criterion to eliminate the requirement of fear, helplessness, and horror at the time of traumatization; the addition of a symptom cluster (negative cognitions and mood); and changes in re-experiencing criteria.[1, 2]

Fear conditioning principles can be applied to trauma or to a stress-related event, given that UCR can be elicited by stimuli that are similar (i.e., CS) to those present at the time of trauma (US; e.g., sights, sounds, smells, context).[9, 2] The goal of exposure-based treatments is to extinguish the conditioned fear trace of the trauma memory by presenting CS without aversive stimuli, thereby signaling safety in anticipation of establishing a dominant extinction memory trace. Clinicians should take additional factors into account when administering exposure-based treatments, including time of day, cognitive resources dedicated to verbal tasks, and menstrual phase, all of which can affect extinction learning ability.[7, 15-18]

Evidence-Based Treatments and Exposure Therapy

Current treatment strategies for PTSD include mainly psychoeducation, psychotherapy, and pharmacotherapy. The most widely used psychotherapeutic techniques are cognitive processing therapy and cognitive behavioral therapy, including prolonged exposure therapy.

According to Foa and McClean,[19] exposure therapy is designed to encourage patients to approach feared but safe objects, situations, thoughts, sensations, and memories with the goal of reducing fear reactions to those stimuli.[19] Exposure-based therapies include both in vivo and imaginal exposure to trauma-related cues in a safe environment. Through exposure therapy, one can recall a fear memory without an aversive outcome, and habituation to trauma-related cues can occur. Exposure therapy was developed with a sound foundation in classical conditioning theory, which suggests that exposure to the CS—which signals harm—in the absence of an aversive US will diminish the expression of the learned fear response.

Fear-Learning Paradigms and Experimental Methodology

Fear-learning paradigms based on Pavlovian conditioning (as discussed in the preceding section) are clinically salient models for the formation of associations among cues, contexts, and their aversive or neutral outcomes. These paradigms utilize reflexes inherent to mammals to imitate learning, extinction, and recall information about safety and danger to assess such fear-learning mechanisms as fear acquisition, fear extinction learning, and fear extinction retention. The following methods of inducing fear learning can produce data that may be useful for identifying risk factors for trauma- and stressor-related disorders. These research methods have implications for informing post-trauma treatment and projecting its success.

Key Concept: *Fear-potentiated startle*—psychophysiological technique for assessing the acoustic startle reflex in traumatized populations. Used as a paradigm for measuring and inducing fear learning.[20]

Fear Acquisition:

Fear acquisition refers to the formation of an association between a previously emotionally neutral stimulus and an aversive outcome after repeated pairings with the outcome. This can be modeled in humans, for example, using a colored shape on a screen and an air blast to the larynx;[20] in rodents, it has been modeled using a colored light and a mild shock to the foot.[21, 22] Researchers can induce fear acquisition in their subjects by repeatedly pairing the neutral cue with the aversive outcome. The number of pairings required for successful fear conditioning is species-specific. Success is defined as the point at which the presentation of the previously neutral stimulus alone elicits a fear response, even in the absence of the aversive outcome. A traumatic event can be conceptualized as a brief, compressed, and robust fear acquisition session.[9] For example, a military service member may have been a passenger in a vehicle that was struck by an improvised explosive device disguised as a pile of garbage. According to the principles of fear conditioning, the garbage may acquire the properties of a CS through its association with the explosion, an aversive stimulus that on its own elicits fear without any learning or associations being made. To the service member, an association is made between the garbage (neutral cue) and the aversive outcome (explosion) coupled with the fear reaction it causes (panic, racing heart, defensive posture). In both experimental (fear conditioning) and experiential (traumatic event) situations, innate neural fear circuitry is activated and can be readily observed and measured using translational neuroscience methods.

Fear Extinction:

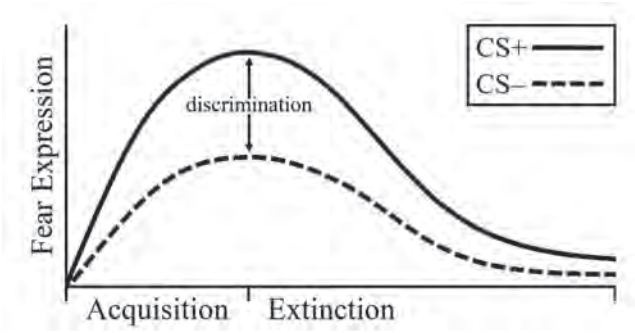
After fear acquisition has been induced successfully, fear memories can be actively recalled and their expression modified through controlled experimental conditions. Through the process of fear extinction, the expression of learned fear responses can be diminished when the previously reinforced CS is presented repeatedly without the corresponding US. The central role of fear extinction learning as an underlying mechanism for the expression of fear-related PTSD symptoms has been thoroughly reviewed by several authors.[7, 8] This area of study has spawned further investigation of the degree to which human populations extinguish previously acquired fear and how quickly acquired fear can be extinguished. Heterogeneous patterns of extinction have been observed recently and represent new avenues for investigating the development, maintenance, and treatment of PTSD. For example, in an individual has been traumatized and/or diagnosed with PTSD, the extinction learning profile might appear to be protracted, slow, or even nonexistent; as such, it may appear to be represent an impairment or absence of an ability to extinguish fear memories. Impairment in the ability to extinguish a fear-potentiated startle due to a high level of fear (termed fear load) during the early phases of extinction has been observed in PTSD cases.[6]

In recent years, translational studies have been undertaken to improve our understanding of the relationship between heterogeneous profiles of extinction learning and differential responses to cognitive behavioral treatments for PTSD. For example, Galatzer-Levy and colleagues[3, 23] have used statistical *latent growth mixture modeling* (LGMM) to suggest that fear extinction profiles may underlie the heterogeneity of PTSD symptom severity over time. This team identified three possible trajectories

of extinction patterns: a rapid decrease in fear (i.e., adaptation with passing symptoms or resiliency), a slower reduction in fear over time (i.e., remission and recovery), and failure to extinguish fear (i.e., absence of symptom remission). The LGMM model was adapted from work by Muthen and others to distinguish patterns of change over time and to identify distinct rates of fear extinction learning.[24] By grouping the data into the categories of rapid, slow, and failure to extinguish, these researchers sought to improve consistency with extinction profile differences among humans. Methods such as these support clinical objectives, e.g., by predicting trajectories of chronic pathology and resiliency.

Key Concept: *Heterogeneity*—variety in characteristics seen in clinically relevant subpopulations ("classes") with finite distributions of longitudinal behavioral measures resulting from genetic, epigenetic, and/or environmental conditions.[3]

Figure 1:
Schematic Representation of Conditioned Fear Expression as a Function of Fear Conditioning Paradigms, Including Fear Acquisition and Fear Extinction



Shown are expected trajectories of fear response when the subject is presented with a reinforced conditioned stimulus (CS+; danger cue) and a nonreinforced conditioned stimulus (CS-; safety cue). The ability of psychiatrically healthy controls to discriminate between the CS+ and CS- based on the magnitude of their fear expression (e.g., fear-potentiated startle) during fear acquisition is significant. Conditioned fear responses to the previously reinforced CS+ diminish over time because the stimulus is presented without an aversive unconditioned stimulus (US) during fear extinction. Adapted from Norrholm et al.(2006; 2008).

While extinction learning refers to a within-session decrease in conditioned fear responses, extinction recall or between-session extinction tests the ability of the individual to retrieve the extinction memory and express this memory by overcoming the original fear memory over time.[25, 26] Tests of extinction recall, also termed retention, allow investigators to determine if a conditioned fear response remains at an extinguished level over time or if it has returned. **Even after extinction has occurred, the original fear memory can return and be expressed in one of three ways: (1) reinstatement (the return of fear after extinction due to the presentation of an aversive outcome); (2) renewal (the return of fear due to a change in context); or (3) spontaneous recovery (the return of fear due to the passage of time).** Between-session extinction indicates spontaneous recovery. If extinction has not occurred—which is likely in an individual with chronic PTSD—then fear expression will not "return" but will remain evident through the demonstration of fear maintenance. By tapping into these mechanisms, researchers have found that fear memories are not erased by extinction but, rather, through competition with new extinction memories.[27, 28] Notably, fear and extinction learning are highly dependent on context. They have been seen in both rodents and humans and probably occur as a result of hippocampal-dependent processes. The neural circuits involved in context processing have been investigated extensively, largely through studies of associative learning.[29-32] These studies have revealed that the hippocampus plays a critical role in contextual learning and memory.[33]

Key Concepts:

a) *Renewal*—return of fear expression after extinction has occurred due to a shift in environmental context.

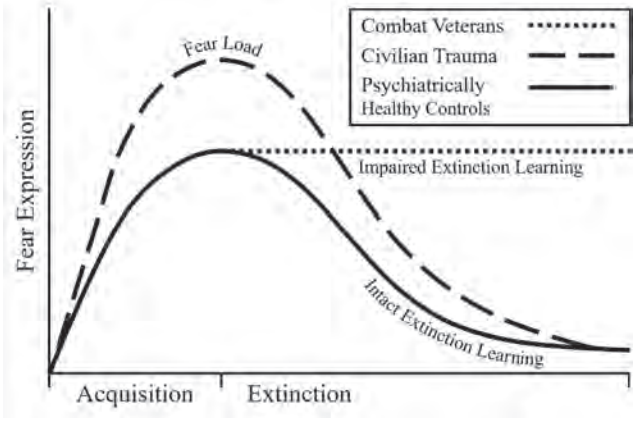
b) *Spontaneous recovery*—return of fear expression due to the passing of time after extinction has occurred.

c) *Reinstatement*—cue-dependent return of fear expression after extinction has occurred.

Fear Inhibition:

The amount of fear expression during late extinction learning is thought to be related to impaired fear inhibition. Inhibition is best predicted by fear responses to a safety signal (CS-) at the end of fear acquisition and is based on the notion that extinction learning is a form of fear inhibition.[9, 34, 35] Jovanovic and colleagues used a fear inhibition transfer task to explore this phenomenon.[36] They first paired a neutral stimulus with a cue associated with an aversive outcome (AX+) then paired a different neutral stimulus with a cue that was not associated with an outcome (BX-). Finally, they paired unique elements of the first and second cues (AB). In healthy participants, the inhibitory properties of the safety cue B were transferred to the danger cue A, such that the fear-potentiated startle was reduced when the individual was presented with stimulus AB compared with AX. Individuals with PTSD failed to transfer inhibition in the presence of similar potentiated startle responses to both the AX and AB stimuli. Based on these results, the investigators suggested that individuals with PTSD demonstrate impairment in their ability to transfer learned safety compared with trauma-exposed individuals without PTSD.

Figure 2:
Schematic of Fear Extinction Learning Profiles of Combat Veterans With PTSD (Dotted Line),[34] Civilians With PTSD (Dashed Line),[6] and Psychiatrically Healthy Controls (Solid Line).[20,28]



Putative Neurobiological Mechanisms of Impaired Fear Extinction

The neural mechanisms and circuitry of fear have been widely studied and documented. Brain structures implicated in rodent and human fear circuitry include the extended amygdala, which is vital for fear expression, and the *ventromedial prefrontal cortex* (vmPFC) and hippocampus, with which the amygdala interacts.[37, 38] In psychiatrically healthy individuals, fear responses are mediated by the amygdala, which is then inhibited by the prefrontal cortex after repeated exposure to a CS without a US (i.e., extinction learning occurs). Rauch and others developed a model of neurocircuitry in individuals diagnosed with PTSD,[37] in which the amygdala is hyperresponsive to threat-related stimuli and the ability of the vmPFC to inhibit amygdala output is impaired.[37, 39, 40] After fear extinction has occurred, the hippocampus and infralimbic cortex/vmPFC complex send inhibitory signals to the amygdala to reduce the expression of conditioned fear through afferent projections from the amygdala to the sympathetic arousal systems.[41, 42]

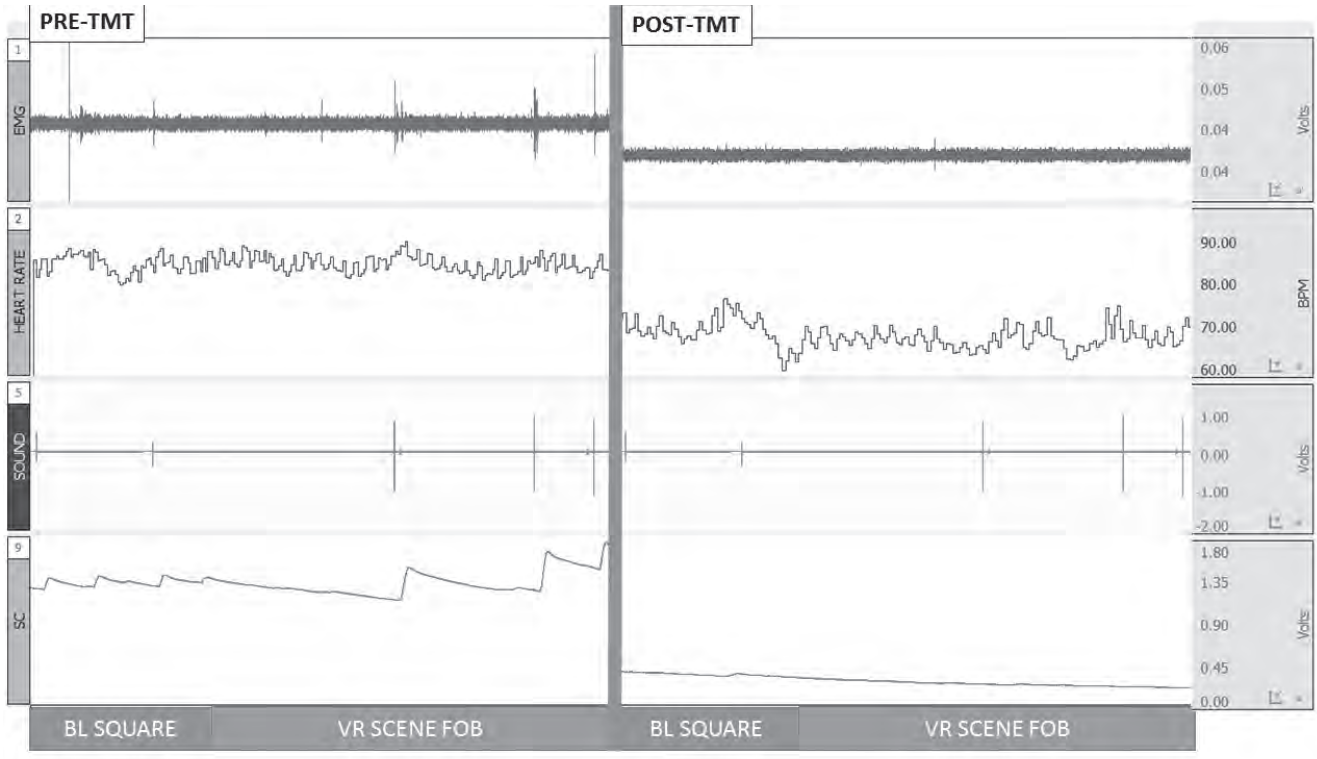
The amygdala plays a role in mediating symptoms of hyperarousal and emotional memory, which is consistent with the heightened emotional memory surrounding traumatic events. By contrast, the hippocampus can signal safe or dangerous contextual stimuli. Thus, the hippocampus can modulate the expression of a fear memory by providing input to the infralimbic cortex (seen in rodents) and the vmPFC (seen in humans).[38, 41-43] The hippocampus has also repeatedly been found to be smaller in patients with PTSD, although it is not known whether this is a risk factor for PTSD or a result of the disorder.[44-46] Functional neuroimaging results from studies by Rubin and colleagues provide additional support for the hypothesis that the baseline hippocampal volume is larger in patients with PTSD who respond to treatment consisting of prolonged exposure and in trauma-exposed resilient individuals compared with patients who do not respond to this treatment.[47] Additionally, neuroimaging studies have revealed hyperactivity in the amygdala and hypoactivity in the prefrontal cortex in patients with PTSD while they are presented with fear stimuli (e.g., films with traumatic scenes).[48] Thus, the neural basis for impaired extinction includes alterations in both functional and structural neuroanatomy.

Key Concept: Memory consolidation is the process of transforming memory (e.g., fear memory) from a labile state immediately after acquisition to a more permanent state that occurs over time. This process has been the target for nonpharmacological attempts to facilitate fear extinction and prevent the return of conditioned fear in humans.[9]

Integration of Laboratory and Clinical Methodologies: Case Study

New applications of psychophysiology in the PTSD clinic have yielded positive results and an exciting avenue for pursuing objective measures of symptom progression and treatment outcomes. Figure 3 presents data traces for a 44-year old African American woman with a history of sexual assault while serving in the military. She was presented with virtual reality-based contexts consistent with her trauma history. Her heart rate, acoustic startle, and skin conductance responses during the presentation of trauma-related cues and contexts (NOTE: without any reference to a perpetrator) were obtained before and after a 10-week course of extinction-based, prolonged-exposure treatment. In parallel with the reported reduction in PTSD symptoms, as indicated on the *Clinician Administered PTSD Scale* (CAPS), her psychophysiological responses to trauma-related cues were markedly diminished following treatment as well. The observation and measurement of objective physiological

Figure 3:
Heart Rate, Acoustic Startle, and Skin Conductance Responses During the Presentation of Trauma-Related Cues and Contexts Were Obtained From A 44-Year-Old Female Abuse Victim Before and After a 10-Week Course of Extinction-Based, Prolonged-Exposure Treatment



TMT = treatment
EMG = electromyogram
SC = skin conductance response
BL SQUARE = baseline measurement without virtual reality stimuli on screen
VR = virtual reality scene
FOB = forward-operating base scenario.

indices of fear and anxiety represent a valuable, complementary clinical tool for mental health providers treating PTSD across traumatized populations.

Clinical Considerations Based on Research Findings

Despite the prevalence of exposure therapy for patients with PTSD and its efficacy in alleviating symptoms, this method does not eliminate the memory trace of traumatic experiences. Indeed, the memory trace has been found to be more robust than fear extinction memory when this modality is used.[56] Fear extinction creates a "safety" memory trace that dominates over the fear memory trace; however, various cues can cause conditioned fear to return. Mechanisms that can be used to determine whether the trauma memory trace still exists, even after extinction learning has occurred, include context-, temporal-, and cue-dependent stimuli. For example, if an individual relocates, s/he may be faced with new stimuli that are similar to those that were present at the time of fear acquisition; this could result in renewal of the "danger" memory trace. Additionally, if enough time passes after extinction learning (treatment) has occurred, then the fear memory could return (clinical relapse) through spontaneous recovery. Finally, the re-introduction of stress (e.g., an additional deployment) could lead to reinstatement of the fear memory and overpower the extinction memory trace.

The effectiveness of exposure therapy and pharmacotherapy in extinguishing conditioned fear may soon be enhanced by newly identified neurobiological factors discovered through translational research. Therapeutic success rates in altering fear extinction may be enhanced by other newly emerging factors, including genetic polymorphisms, menstrual cycle phase, hormone levels, sleep patterns, and comorbid disorders which may interfere with treatment.[7, 15-18, 57, 58]

Genomic Effects on Extinction Learning

Pharmacological research designed to enhance fear extinction learning has been focused on the effects of manipulating neurotransmitters and other neural signals, many of which have complex relationships with PTSD risk and clinical presentation.[49, 50] Singewald and colleagues explored the effects of manipulating brain-derived neurotrophic factor (BDNF), serotonin, and norepineprine, which are all essential for regulating fear and stress-related systems. In studies of a BDNF polymorphism (val66met), met allele carriers showed impaired fear extinction learning, increased vmPFC activity, and decreased amygdala activity during extinction learning and had a worse response to exposure therapy compared with homozygous val/val allele carriers. These findings, coupled with those of translational animal studies, implicate altered BDNF signaling as a potential risk factor for altered fear expression and inhibition in humans and as a target for pharmaceutical intervention.[7, 51-53] Importantly, enhanced norepinephrine signaling has also been shown to result in more efficient fear extinction learning retrieval and retention.[49]

As highlighted in several studies,[7, 54] specific genotypes may not be directly involved in the etiology of a disorder but, rather, may interact with environmental influences to increase the likelihood of posttraumatic sequelae.[7, 54] Kilpatrick and colleagues observed, for example, that a significant interaction among a putative "risk" allele in the gene coding for the serotonin transporter (the "short" allele of 5-HTTLPR), high hurricane exposure in Florida, and low social support could be used effectively predict a diagnosis of PTSD.[55]

Pharmacotherapy

Two main goals of pharmacotherapy for PTSD are (1) to reduce the risk of PTSD immediately after trauma exposure, and (2) to treat PTSD in its clinical presentation. Risk and resiliency factors have been shown to mediate the biopsychosocial effects of trauma exposure and subsequent success of pharmacological treatment. In 2004, the pharmacy records of the US Department of Veterans Affairs showed that most veterans (80%) diagnosed with PTSD received psychotropic medication.[59]

Pilot studies suggest that *methylenedioxymethamphetamine* (MDMA) may also be used in conjunction with psychotherapy as a catalyst for extinction learning in patients with chronic treatment-resistant PTSD.[60] The only pharmacological treatments currently approved by the US Food and Drug Administration for PTSD are selective serotonin reuptake inhibitors. As a result, relevant research on MDMA is limited to preclinical trials.[60] As a result, much more research is needed before MDMA can be considered a clinical pharmacological intervention for PTSD.

Key Concept: *Risk and resiliency factor*—characterization that mediates (predicts or diminishes) vulnerability to a condition.

Contributing Factors: Sex, Menstrual Cycle, and Sleep Patterns:

Translational studies of fear learning often exclude female subjects because of the inherent variability associated with dynamic hormone levels and other sex differences. There is reason to believe, however, that estrogen has a marked effect on extinction learning and retention.[16, 61, 62] **Extinction memory has been shown to be sexually dimorphic and dynamic across menstrual cycles.**[63, 64] Additionally, short-term administration of estrogen has been shown to mediate synaptic plasticity within the extinction network.[65, 66] Several hypotheses have been posed to explain these estrogen-related effects. For example, the observation that **estrogen receptors are highly expressed in the amygdala, hypothalamus, and hippocampal cortical regions, which are included in neurobiological models of PTSD,**[16] may explain why higher levels of estrogen appear to have a *protective* effect, facilitating extinction and influencing PTSD symptom severity. Conversely, women with low estrogen levels and high PTSD symptom severity tend to express higher levels of fear and less robust extinction.[15] The dynamic nature of the menstrual cycle and accompanying changes in sex hormone levels has a particularly strong influence on fear extinction processes; indeed, the level of estrogen at the time of trauma or exposure therapy could shape the subsequent trajectories of PTSD symptom development and the ability to extinguish fear memories.[15, 67] Thus, being able to identify naturally cycling endogenous sex hormones in populations at risk for trauma exposure could help researchers develop preventative measures.

Sleep is another natural cycling phenomenon that can have profound effects on health and wellbeing. Unfortunately, the role of sleep in consolidating fear memories is less well understood than the role of the menstrual cycle. Both circadian and time-of-day effects have been assessed by the Pace-Schott team,[64] which found that extinction learning and generalization of extinction recall are significantly better in the morning compared with later time points during the day. These findings, although promising, require replication to be interpreted and implemented clinically. The relationship between sleep deprivation and fear extinction learning has been more widely studied, because sleep loss often accompanies PTSD. According to Zuj et al.,[7] extinction learning ability is impaired in PTSD patients as a result of sleep deprivation. In their studies of the effect of sleep on both fear memory acquisition and extinction, Pace-Schott and colleagues found that inadequate sleep might hinder fear extinction processes.[64] Specifically, they found these two processes use similar neurological structures in the limbic system, as well as *N-methyl-D-aspartate* (NMDA)-dependent consolidation processes. Thus, interactions between fear and extinction circuitry are

likely to take place during sleep-dependent consolidation. They may also interact competitively during retrieval; this may account for the lack of extinction memory enhancement in total sleep-deprived individuals compared with rested individuals following exposure to an extinguished cue prior to testing.[68] Based on their findings in murine studies, Fu and colleagues proposed that REM sleep in particular may enhance NMDA-dependent consolidation of extinction memory and lead to increased safety memory consolidation and safety/danger cue discrimination during wakefulness.[69] Together, these findings should inform future research on sleep concurrent with therapy to improve both treatment outcomes and sleep quality.[70]

Reversal Learning and Context-Cue Processing

Most clinical researchers and practitioners rely on the *DSM-5* as a guide for making psychiatric diagnoses. Over the course of the *DSM*'s history, however, the diagnostic criteria for numerous disorders have been eliminated, added, and modified considerably. Furthermore, translational research into the underpinnings of mental disorders often reveals the need to consider trans- and epidiagnostic factors.

It is critical for healthcare professionals working with patients with PTSD and similar disorders to keep abreast of changes in the criteria for identifying these disorders. Fear may be a central feature of PTSD; in fact, it can be modeled using fear conditioning.[9] PTSD is not defined as a fear-conditioning disorder, however, or even as a fear-centric disorder. The clinician would have to know if all of the current diagnostic criteria for PTSD have been met in each patient; otherwise, a key outcome of trauma exposure could be overlooked, i.e., lasting cognitive deficits in cue-context association processing. Levy-Gigi and Richter-Levin[71] suggest that a paradigm can be used to assess the hidden costs of trauma exposure in nonclinical populations.[71] By incorporating the cue-context relationship into a fear-learning paradigm, they were able to assess the patient's skills in "reversal learning."

Key Concept: *Cue-context reversal learning*—reversing the expected valence of outcomes after presenting cue- and context-related information.

Participants learned that the valence of a cue-context pair that initially predicts a neutral or aversive outcome may predict a different outcome in the future when either the cue or context changes. To learn the new associations tested in the paradigm successfully, participants needed to reverse the association of either the original cue or the original context, keeping the valence of the other dimension constant to isolate the reversal of a single dimension (cue OR context). The experimental group included trauma-exposed firefighters and crime scene investigators (CSIs); the control group consisted of civilians with no trauma exposure. The investigators found a significant interaction between each group and each reversal type of interaction: Firefighters had difficulty learning that a context predicting a negative outcome could also predict a positive outcome if paired with a different cue in the future; **CSIs showed selective impairment in reversal of a cue that initially predicted a negative outcome; and trauma-naïve civilians had no difficulty with this paradigm.**

It was hypothesized that that the firefighters had difficulty with this task because they are required to notice contextual information for their occupation (e.g., making contextual observations to determine the location of potential victims in a burning building). By contrast, CSIs are required to notice smaller cues and details involved in investigations, which may prepare them to predict which *cues* will result in negative outcomes. Thus, people who are trained to do specific tasks may be at greater risk for PTSD when those tasks are associated with trauma. Firefighters, for example, may experience distress during their day-to-day lives because of impaired cognitive processing. If a firefighter were called to put out a fire in House A (context) with billowing smoke (cue), s/he would likely predict a negative outcome in the form of damage to the house, injuries, etc. If the same firefighter drove by House A (context) one year later and saw chimney smoke (cue) resulting from the safe use of a fireplace (positive outcome), s/he may have difficulty reversing the outcome of that context from a dangerous one to a positive one because it was previously paired with a negative cue. Another clinical application might involve witnessing an explosion in a coffee shop garbage can. In this case, the cue would be the garbage can and the context would be the coffee shop. Being able to associate

a coffee shop with a positive outcome in the future would involve reversal of learning of the context (provided no garbage cans are present in the coffee shop). Being able to associate a garbage can in a park with a positive outcome in the future would be an example of reversal learning of the cue.

In summary, research models of trauma and stress exposure have correlated stimulus-outcome expectancies with clinical outcomes. Some have also demonstrated the possibility of a "hidden price" for repeated trauma exposure that may be worth investigating in nonclinical populations.[71] Preventative clinical interventions may be available for individuals at risk for fear-learning deficits. Thus, it is particularly important to identify such individuals so that contextual cue processing skills can be introduced before they are exposed to trauma. That would reduce the possibility of high-risk individuals developing fear-learning deficits.[46] There is a clear need to address fear-learning deficits, even among those who have not been diagnosed with a disorder like PTSD, if the individual has been exposed to trauma. This novel study also implicates occupation as a factor to consider when developing treatment plans, because the individual's occupation may provide clues indicating specific deficits (e.g., reversal learning impairment) and inform the details of exposure during therapy (focusing on cue versus contextual information).

Neurobiology of Context-Cue Reversal Paradigm Performance:

The context-cue reversal paradigm deficits exhibited by individuals who have experienced long-term exposure to trauma can be explained through several neurobiology-based hypotheses. Through their investigation of the relationship between the outcomes of psychotherapy for PTSD and hippocampal size, Rubin and colleagues found that patients with PTSD who had a successful response to treatment and resilient trauma-exposed controls had a greater hippocampal volume at baseline compared with trauma-exposed individuals who did not have a successful treatment outcome.[47] Furthermore, the baseline hippocampal volume was not significantly different in patients versus trauma-exposed healthy controls. These findings suggest that the hippocampus plays an integral role in discriminating signals of safety versus danger during exposure to trauma and may be helpful in predicting the outcomes of trauma-focused treatments.[71]

Alternatively, it is possible that several neural mechanisms are active simultaneously during context-cue reversal learning. The observation that CSIs and firefighters show different selective impairments in reversal learning supports the hypothesis that one neural mechanism is responsible for context-related outcomes and another is responsible for cue-related outcomes. The extensive body of research associating hippocampal function with contextual processing suggests that context-related fear extinction impairments are related to changes in hippocampal structure and function, which is necessary for distinguishing between contexts that signal safety and those that signal a threat.[44, 72] Cue-related impairments, on the other hand, may reflect amygdala dysfunction; this possibility is supported by the findings of murine amygdala lesion studies that resulted in impaired cue-conditioning.[73] Last, left *inferior parietal lobe* (IPL) activity has been implicated as a biomarker of re-experiencing symptoms among patients with PTSD.[46] Specifically, the left IPL has been implicated in contextual cue processing.[74] Pretreatment levels of left IPL activation indicated the degree of improvement in symptoms, particularly re-experiencing symptoms.[46, 74] Neuroimaging techniques, such as functional magnetic resonance imaging, could lend more insight into the neural mechanisms governing cue- and context-associated learning and allow us to identify risk factors for fear learning impairments.

Conclusions

As clinical investigators continue to explore the neurobiology underlying trauma- and stressor-related disorders such as PTSD, it is vital to consider the wide array of literature supporting psychophysiological measures that can be used to predict clinical risk factors and treatment outcomes. Although PTSD is not defined as a fear-centric or fear disorder, fear-learning mechanisms comprise an integral component of this and related disorders. Notably, assessments of fear learning, extinction, recall, and retention have indicated new discoveries about the behavioral, cognitive, and neurobiological moderators and mediators of the psychophysical effects of trauma. Variability in fear extinction learning and retention may eventually serve as a predictor of clinical pathology or resilience that can be

used in the future to develop individualized treatment for trauma-related disorders. New forms of pharmacotherapy—including MDMA, D-cycloserine, and sex hormones—have the potential to aid and expedite the development of treatment modalities for those who may be resistant to traditional exposure therapies or those who are identified as being at risk. **Additionally, new forms of exposure therapy, including virtual reality exposure, may serve as more effective extinction facilitators by increasing engagement.** Risk factors for the inability to extinguish fear memories could include genetic, sleep hygienic, hormonal, or cognitive factors that have been identified as biomarkers of extinction-learning deficits. Finally, improvements in our understanding the psychophysiological and neurological underpinnings of PTSD, trauma-related disorders, and other anxiety disorders may guide the development of diagnostic criteria and effective treatments in the future. Most importantly, these and future findings may be used to improve the quality of life for patients by fostering discussions among clinicians that can result in the tailoring of psychological and pharmacological treatments for a successful outcome.

Appendix

Key Definition and Concepts	
Memory consolidation	The process of transforming a memory (e.g., fear memory) from a labile state immediately after acquisition to a more permanent state that develops over time. This process has been a target for non-pharmacological attempts to facilitate fear extinction and prevent the return of conditioned fear in humans[9]
Intermediate phenotype	A trait that represents fundamental neurobiological mechanisms related to the etiology of clinical presentations of an illness[7, 61]
Fear-potentiated startle	A psychophysiological technique for assessing the acoustic startle reflex in traumatized individuals. Used as a paradigm to measure and operationalize fear learning[11-12, 21-22]
Heterogeneity	Clinically relevant subpopulations (“classes”) within finite distributions in longitudinal behavioral measures due to genetic, epigenetic, and/or environmental conditions[3]
Risk and resiliency factors	A characterization that mediates (predicts or diminishes) vulnerability to a condition[9]
Biomarker	A measurable indicator of a healthy or pathological biological process. It may be used to identify vulnerability to a disorder or the efficacy of preventive interventions. For example, biomarkers have been used to link fear-learning deficits to PTSD symptoms[7,10, 61]
Renewal	A return of fear expression after extinction has occurred due to a shift in environmental context. For example, moving to a new location may be associated with return of PTSD symptoms after successful exposure therapy has occurred[30-33]
Spontaneous recovery	A return of fear expression associated with the passage of time after extinction has occurred. For example, after a long period of time, the successful outcomes of PTSD therapy may be overrun by a return of symptoms[31]
Reinstatement	A cue-dependent return of fear expression after extinction has occurred. For example, if stress induced the re-introduction of fear acquisition, memory traces may outcompete fear extinction[29]
Cue-context reversal learning	Reversing the expected valence of outcomes after presenting cue- and context-related information[71]

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Multiple-Choice Questions

29. All of the following are a form of return of fear after extinction, *except*:

A. Renewal.

B. Reinforcement.

C. Spontaneous recovery.

D. Reinstatement.

30. Based on your reading of this lesson, what is the rationale that explains enhanced treatment using *virtual reality exposure* (VRE)?

A. VRE helps the patient remember the trauma.

B. VRE elevates physiological arousal, thereby increasing engagement with treatment.

C. VRE is entertaining for the patient.

D. VRE is less invasive than traditional exposure therapy techniques.

31. Evidence currently exists for a role for each of the following biological factors in extinction learning and exposure therapy outcome, *except:*

A. Fluctuations in gonadal hormones throughout the menstrual cycle.

B. Sleep hygiene.

C. Age at the time of treatment.

D. Hippocampal volume.

32. Based on the context-cue association paradigm detailed in this lesson, which of the following occupations may cause a trauma-exposed individual to have trouble reversing the danger signal of a context?

A. Criminal-scene investigator

B. Paramedic

C. Coroner

D. Emergency room surgeon

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Best Practices in CME

Competing With Learned Fear: Implications of Fear Extinction for Clinical Intervention

By Leah Weingast; Haley E. Haas; Seth Davin Norrholm, PhD

ID#: L003411

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Objective psychophysiological measures of fear learning, specifically fear extinction, can be used to operationalize the fear-related symptoms of trauma- and stressor-related disorders such as PTSD. These symptoms can be thought of as a failure to inhibit fear, which can arise after trauma and can be moderated by intermediate phenotypes and biomarkers. Psychophysiological assessments might also be used as a tool to predict clinical risk factors and treatment responsiveness. Treatment for trauma-related disorders should take into account new discoveries about the behavioral, cognitive, and neurobiological mediators of the psychophysiological effects of trauma. Specifically, variability in fear extinction learning has major clinical implications for the future of individualized pharmacological and nonpharmacological treatments.

Key Point 1: Fear Learning Informs Treatment

A better understanding of the principles of fear learning in humans may provide alternative and more effective treatment strategies for PTSD. The available literature suggests that more effective treatment strategies may include both pharmacological and non-pharmacological enhancement of extinction learning.

Key Point 2: Fear Learning is Heterogeneous

Heterogeneity of fear learning may represent intermediate phenotypes and biomarkers that moderate and mediate fear learning and PTSD symptomatology in traumatized individuals

Key Point 3: Psychophysiology Assessment Implications

Psychophysiological assessments may inform both translational science moving forward, as well as the treatment of trauma-, stressor-, and anxiety-related psychiatric disorders.

Notes

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Internet and Gaming Disorder and Associated Changes in the Brain

Aviv Weinstein, PhD

No commercial support was used in the development of this CME lesson.
Off-label use of escitalopram and bupropion is discussed in the treatment section of this lesson.
These medications are not FDA approved for treatment of the disorder indicated.

KEY WORDS: Internet gaming disorder • Brain imaging • *functional MRI* (fMRI) • Dopamine reward system

LEARNING OBJECTIVES: Clinicians will (1) review recent evidence of *internet gaming disorder* (IGD) on brain imaging studies; (2) describe how structural and functional brain imaging studies—including studies of grey matter volume, and white matter density, functional connectivity, executive function, reward and craving—can be used to identify IGD comorbidity with other psychiatric disorders; and (3) explore data on the biological basis for categorizing IGD as a behavioral addiction.

LESSON ABSTRACT: Recent *functional magnetic resonance imaging* (fMRI) studies in patients with IGD have shown reduced gray matter volume in regions in the brain associated with attention, motor coordination, executive function, and perception. In adolescents, reduced white matter integrity was found in regions involved in decision-making, behavioral inhibition, and emotional regulation, with disruption in functional connectivity in areas responsible for learning memory; executive function; processing of auditory, visual, and somatosensory stimuli; and relaying sensory and motor signals. These patients also demonstrated decreased functional connectivity among prefrontal cortex/striatal circuits, an increase in risk-taking choices, and impaired ability to control impulses, which is similar to characteristics of patients with other impulse control disorders. Recent study findings suggest a relationship between IGD and *attention-deficit/hyperactivity disorder* (ADHD), in that ADHD-related changes in executive control mechanisms may predispose to IGD and, conversely, increased IGD-related functional connectivity among several executive control brain regions may contribute to comorbidity with ADHD and depression. The behavioral addiction model of IGD is suggested through structural and functional changes in the mechanisms of reward and craving (but not withdrawal). Further study of white matter density and functional connectivity is needed to validate these findings and to explore similarities between IGD-related neurochemical and neurocognitive brain circuits and ADHD and depression.

COMPETENCY AREAS: This lesson addresses the gap in our understanding of changes in brain mechanisms that contribute to the development of IGD, which often goes underreported by adolescents and their families. Upon concluding this lesson, the clinician will be able to describe the neural mechanisms underlying IGD and assess and manage this disorder.

Introduction

The Diagnosis and Brain Imaging of Internet Gaming Disorder:

Internet gaming disorder (IGD) involves excessive or poorly controlled preoccupation, urges, or behaviors regarding computer video game playing that leads to impairment or distress.[1] IGD falls in the category of behavioral addiction, in that individuals with this disorder exhibit excessive use despite adverse consequences, withdrawal phenomena, and tolerance—all of which are characteristic of substance use disorders. There is a debate over the best clinical term for internet addiction. Young (1998; 2009) argued that IGD demonstrates a loss of control over gaming;[2-3] others have suggested that IGD is an impulse control disorder[4] or a component of an obsessive-compulsive disorder (OCD).[5] In the *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition* (DSM-5),[6] IGD is identified in Section III as a condition warranting further clinical research and experience before being considered for inclusion as a formal disorder. The area of brain research in IGD has been expanding rapidly, particularly with the use of brain-imaging studies[7-12] and particularly in adolescents. We have summarized the findings of key studies herein in an attempt to close current gaps in clinical knowledge of brain imaging evidence of IGD.

Brain Imaging Studies of the Resting State in IGD

Excessive internet game use has been associated with abnormal resting state activity in regions of the brain that are responsible for impulse control, reward processing, and somatic representation of previous experiences.[13] Adolescents with IGD have also shown higher rates of global cerebral blood flow into areas that are important for learning and memory (amygdala/hippocampus), conscious urges to use drugs (insula), executive function, and inhibition.[14] Individuals with IGD have shown enhanced homogeneity in brain regions governing sensory-motor coordination[15-16] and decreased homogeneity in brain regions governing visual and auditory functions.[15] **Synchronization among these regions with the frontal lobe supports the hypothesis that reward pathways are enhanced in individuals with IGD.[17] Patients with either** IGD or *alcohol use disorder* (AUD) have shown increased regional homogeneity in the *posterior cingulate cortex* (PCC), which is associated with attention, future planning, and retrieval of autobiographical memories, whereas only patients with IGD have demonstrated reduced homogeneity in the superior temporal gyrus, which is associated with auditory processing and language.[18] Internet addiction severity scores correlate with the degree of homogeneity in the medial frontal cortex, precuneus/PCC, and left inferior temporal cortex in patients with IGD.[18] An additional distinction between IGD and AUD was provided by a recent study of resting-state quantitative electroencephalography patterns in IGD and AUD,[19] which showed that a lower absolute beta power may be a marker for IGD versus a higher absolute power in the delta band for AUD. This provides neurophysiological evidence that IGD is a behavioral addiction distinct from AUD.

Summary: Preliminary evidence of cognitive function in IGD has been provided in resting-state studies. Thus far, however, only one study has provided evidence of how IGD develops.[18]

Studies of the Brain's Gray Matter Volume and White Matter Density

Early *functional magnetic resonance imaging* (fMRI) studies showed a greater volume of gray matter in the left striatum in participants with IGD compared with control participants. **Using the *Cambridge Gambling Task*[20]—a decision-making task used to clarify the relationship between brain function (i.e., decision-making) and structural changes in reward centers of the brain—investigators found that grey matter volume correlated negatively with deliberation time. Grey matter density was lower in areas of the brain involved in urges and the regulation of emotional behavior;[21] the cause of this difference could not be inferred from the study findings.** In pro-gamers, the grey matter volume was increased in areas associated with attention and sensory-motor coordination.[22]

Studies of white matter density in adolescents with IGD revealed a reduced density in several regions of the brain (*orbitofrontal cortex* [OFC], corpus callosum, cingulate, inferior frontal-occipital fasciculus, and the

internal and external capsules of the corona radiata)[23] and an increase in the thalamus and left PCC. The higher density in the thalamus was associated with increased severity of IGD.[24]

The gray matter volume was reduced in frontal brain regions; the white matter volume was reduced in the parahippocampal gyrus and internal capsule.[25] Gray matter atrophy was also reported in areas involved in cognition and motor control, and white matter density was reduced in areas involved in cognitive planning and cognitive control.[26] These findings suggest an association between gray matter atrophy/white matter density loss and the duration of video game playing that can be used to assess the effects of the duration of playing on the degree of white matter atrophy. Finally, **gray matter density was lower in brain regions that are involved in decision-making**, **behavioral inhibition, and emotional regulation in IGD,** whereas white matter density was reduced in the inferior frontal gyrus, insula, amygdala, and anterior cingulate.[27]

Summary: There is preliminary evidence of structural changes in gray matter volume and white matter density in individuals with IGD. Changes in gray matter volume are seen consistently in such structures as the anterior cingulate, supplementary motor areas, cerebellum, insula, and the inferior temporal gyrus.[12] Few studies have consistently shown changes in white matter density in several brain regions in IGD.

Recent Studies in Young Adults and Adolescents

Recent studies have shown that adolescents with IGD have lower diffusion measures in areas of the brain associated with attention, impulse control, motor function, and emotional self-regulation.[28] Adolescents with IGD have also been found to have reduced gray matter volume in brain regions associated with attention, motor coordination, working memory, and perception;[29] these findings are compatible with those of previous studies of gray matter volume in IGD.[21, 25-26] By comparing the outcome of changes in the Stroop effect (i.e., measurement of the reaction time) on tasks with grey matter volume, investigators found a negative correlation between the volume of gray matter in the *anterior cingulate cortex* (ACC) and response errors.[29] In adolescents with IGD, the volume of gray matter in the PFC and the amygdala correlated with scores on the *Barratt Impulsivity Scale*, which allows investigators to associate function (impulsivity) with structure (i.e., gray matter volume in the OFC and amygdala).[30] Participants with IGD also exhibited reduced white matter density in the ACC and right *dorsolateral-prefrontal cortex* (DLPC), which are associated with executive functions (such as those measured by the Stroop effect).[31] Increased duration of video game playing was associated with delayed development of the OFC, pallidum, putamen, hippocampus, caudate/putamen, insula, and thalamus, and a higher mean diffusivity in the thalamus, hippocampus, putamen, and insula was associated with lower intelligence.[32] These measures indicate a relationship among the amount of video game playing, intelligence, and brain development, although no causal inference can be made. There is also evidence of reduced white matter efficiency in the frontal cortex, ACC, and pallidum in IGD.[33] An increase in white matter density and decrease in diffusivity were also seen in frontal fiber tracts in patients with IGD.[34]

Summary: Differences in diffusion, grey matter volume, white matter density, and structural development have been identified for adolescents and young adults with IGD compared with non-IGD patients. Differences in function (e.g., the Stroop effect and intelligence) have also been identified that suggest a relationship with the duration of video game playing. Further study if required, however, for replication and validation of these findings. See Table 1 for the results of resting-state and structural studies of IGD.

Table 1:
Resting State and Structural Studies of Internet and Gaming Disorder[1]

Main Findings and Evaluations	Participants—sex and age matched controls	Methods	Citation
Increased activity in the OFC, striatum, and sensory regions. Evaluation: a cross-sectional study with a small number of participants	Internet/gaming over-users (n=11) Controls (n=9)	rCMRglu in PET	Park et al., 2010
Enhanced ReHo in the cerebellum, brainstem, right cingulate gyrus, bilateral parahippocampus, right frontal lobe (rectal gyrus, inferior frontal gyrus, and middle frontal gyrus), left superior frontal gyrus, left precuneus, right postcentral gyrus, right middle occipital gyrus, right inferior temporal gyrus, left superior temporal gyrus, and middle temporal gyrus	College students with IGD (n=19; 8 female) Controls (n=19)	ReHo measure in MRI	Liu et al., 2010
Higher left striatal GM volume Left striatal grey matter volume negatively correlated with deliberation time in Cambridge Gambling Task Activity on the Monetary Incentive Delay task was enhanced during feedback of loss vs no loss	Frequent video game players (n = 76; Mean age: 14 y) Controls: Infrequent age-matched video game players (n = 78)	GM volume measure in MRI	Kuhn et al., 2011
Reduced GM density in the left ACC, left PCC, left insula, and left lingual gyrus	Adolescents with IAD (n = 18; 2 female) Sex-matched controls (n = 15)	GM volume measure in MRI	Zhou et al., 2011
Decreased GM volume in the bilateral DLPFC, SMA, OFC, cerebellum, and left rostral ACC Enhanced FA for left PLIC Reduced FA for WM in right PHG Changes in GM volume in DLPFC, rACC, SMA, and WM FA in PLIC correlated with duration of internet addiction	Adolescents with IGD (n = 18; 6 female) Controls (n = 18)	WM FA changes using DTI in MRI	Yuan et al., 2011
Enhanced ReHo in brainstem, inferior parietal lobule, left posterior cerebellum, and left middle frontal gyrus Decreased ReHo in temporal, occipital, and parietal cortex	IGD (n = 15) Controls (n = 14)	ReHo measure in MRI	Dong et al., 2012
Increased impulsiveness and perseverative errors Increased volume in left thalamus GM Decreased GM volume in inferior temporal gyri, right middle occipital gyrus, and left inferior occipital gyrus	IGD (n = 20) Controls (n = 18 males) Pro-gamers (n = 17)	GM volume measure in MRI	Han et al., 2012
Lower FA in OFC, corpus callosum, cingulate, inferior frontal-occipital fasciculus, and corona radiation (internal and external capsules) FA in left genu of corpus callosum correlates negatively with Screen for Child Anxiety-Related Emotional Disorders score and between FA values in the left external capsule and Young's Internet Addiction Scale	IAD (n = 17; 3 female) Controls (n = 16)	Brain WM integrity measured by DTI in MRI Whole-brain voxel-wise analysis of FA performed using TBSS	Lin et al., 2012
Higher FA in thalamus and left PCC Higher FA in thalamus associated with greater severity of internet addiction	IDA (n = 16) Controls (n = 15)	WM integrity using DTI in MRI	Dong et al., 2012

Main Findings and Evaluations	Participants—sex and age matched controls	Methods	Citation
GM atrophy in the right OFC, bilateral insula, and right supplementary motor area FA reduced in right genu of corpus callosum, bilateral frontal lobe WM, and right external capsule GM volume in right OFC and bilateral insula and FA in right external capsule correlates with Young Internet Addiction scores	IGD (n = 17; 13 female) Sex-matched controls (n = 17)	GM and WM density based on VBM analysis and TBSS	Weng et al., 2013
Decreased cortical thickness in right lateral OFC	Adolescents with IAD (n = 15 males) Sex-matched controls (n = 15)	Cortical thickness in MRI	Hong et al., 2013
Increased cortical thickness in left precentral cortex, precuneus, inferior middle frontal cortex temporal and middle temporal cortices. Decreased cortical thicknesses of left lateral OFC, insula, lingual gyrus, right postcentral gyrus, entorhinal cortex, and inferior parietal cortex. Cortical thickness of left precentral cortex, precuneus, and lingual gyrus correlated with duration of online gaming addiction Cortical thickness of orbitofrontal cortex correlated with impaired task performance during color-word Stroop task	Adolescents with IGD (n = 18) Controls (n = 18)	Cortical thickness in MRI	Yuan et al., 2013
Reduced GM diffusion in right anterolateral cerebellum, right inferior and superior temporal gyri, right SMA, middle occipital gyrus, right precuneus, postcentral gyrus, right inferior frontal gyrus, left lateral lingual gyrus, left paracentral lobule, left ACC, and median cingulate cortex, bilateral fusiform gyrus, insula, PCC, and thalamus Higher GM volume in right inferior and middle temporal gyri, and right PHG Reduced GM volume in left precentral gyrus	IGD (n = 18) Controls (n = 21)	DKI in the detection of GM diffusion	Sun et al., 2014
IGD participants had lower absolute beta power than AUD and healthy control group AUD group showed higher absolute delta power than IGD and healthy control group No significant correlations between severity of IGD and QEEG activities in patients with IGD	IGD (n = 34) AUD (n = 17) Healthy controls (n = 25)	Resting-state QEEG	Son et al., 2015
GM volume of bilateral ACC, precuneus, SMA, SPL, left DLPFC, left insula, and bilateral cerebellum decreased in IGD participants compared with healthy controls GM volume of the ACC negatively correlated with incongruent response errors on Stroop test	IGD (n = 28) Controls (n = 28)	GM volume measured in MRI	Wang et al., 2015
IGD and AUD participants had increased ReHo in the PCC. IGD participants showed decreased ReHo in the right superior temporal gyrus compared with AUD and control participants. Patients with AUD showed decreased ReHo in the ACC. Scores on internet addiction severity positively correlated with ReHo in the medial frontal cortex, precuneus/PCC, and left inferior temporal cortex (ITC) among participants with IGD	16 patients with IGD, 14 alcohol with AUD, and 15 control participants.	Regional homogeneity (ReHo) measure in MRI	Kim et al., 2015
Lower GM density in the bilateral inferior frontal gyrus, left cingulate gyrus, insula, right precuneus, and right hippocampus. Lower white matter density in the inferior frontal gyrus, insula, amygdala, and anterior cingulate. Evaluation: a cross-sectional study with a large number of participants enables GM and WM analysis in IGD.	35 participants with internet gaming disorder and 36 control participants.	GM density and white matter density changes using voxel-based morphometric analysis in MRI	Lin et al., 2015

Main Findings and Evaluations	Participants—sex and age matched controls	Methods	Citation
MD correlated with the amount of video game playing in the left, middle, inferior, and orbital frontal cortex; left pallidum; left putamen; left hippocampus; left caudate; right putamen; right insula; and thalamus in both cross-sectional and longitudinal analyses Increased MD values in left thalamus, left hippocampus, left putamen, left insula, and left Heschl gyrus were associated with lower intelligence	Children 114 boys and 126 girls	DTI mean diffusivity (MD)	Takeuchi et al., 2016
Reduced FA in anterior cingulate Cortex-right DLPFC pathways in IGD	28 IGD adolescents 25 control participants	WM integrity and connectivity	Yuan et al., 2016
Reduced nodal efficiency in frontal cortex, anterior cingulate cortex and pallidium in IGD Global efficiency of WM network correlated with the IAT scores in IGD	16 right-handed adolescents with IGD 16 controls	WM integrity measured with .DTI	Zhai et al., 2016
Increased FA values within forceps minor right anterior thalamic radiation, right corticospinal tract, right inferior longitudinal fasciculus, right cingulum to hippocampus and right inferior fronto-occipital fasciculus (IFOF) decreases in RD value within forceps minor, right anterior thalamic radiation and IFOF relative to control subjects.	181 male patients, including 58 IGD subjects without psychiatric comorbidity, and 26 male control subjects	White matter (WM) integrity and connectivity	Jeong et al., 2016
Compared with the ADHD-only group, the ADHD+IGD group showed lower relative delta power and greater relative beta power in temporal regions The relative theta power in frontal regions were higher in the ADHD only group compared with the HC group Increased neuronal connectivity within the parieto-occipital and temporal regions for the ADHD+IGD group	16 adolescent males with ADHD + IGD 15 adolescent males with ADHD 15 healthy adolescent males	Qualitative EEG	Park et al., 2017
An association between decreased interhemispheric connectivity in the frontal region and vulnerability to attention problems in patients with MDD and IGD Interhemispheric and intrahemispheric coherence value for the alpha band was significantly lower in MDD+IGD than MDD only Intrahemispheric coherence values for the beta band were higher in MDD+IGD than in MDD only Increased intrahemisphere connectivity within any lobe may result from excessive online gaming	14 males with MDD + IGD 15 males with MDD only	Qualitative EEG	Youh et al., 2017

[1]Studies arranged chronologically.

ACC, anterior cingulate cortex
ADHD, attention-deficit/ hyperactivity disorder
AG, angular gyrus
DKI, diffusional kurtosis imaging
DLPFC, dorsolateral prefrontal cortex
DTI, diffusion tensor imaging
FA, fractional anisotropy
GM, grey matter
IAD, internet addiction disorder
IFOF, inferior fronto-occipital fasciculus
IGA, internet gaming addiction
IGD, internet gaming disorder
MD, mean diffusivity
MDD, major depressive disorder
MPFC, medial prefrontal cortex
OFC, orbitofrontal cortex
PCC, posterior cingulate cortex
PHG, parahippocampal gyrus
PLIC, posterior limb of the internal capsule
QEEG, quantitative electroencephalography
ReHo, regional homogeneity
SMA, supplementary motor area
SPL, superior parietal lobule
STG, superior temporal gyrus
TBSS, tract-based spatial statistics
VBM, voxel-based morphometry
WM, white matter

Cortical Thickness:

Two fMRI studies of cortical thickness produced conflicting measures in several regions of the brain in adolescents with IGD, with one indicating an increase in thickness and the other a decrease in thickness.[35-36] The cortical thickness of the OFC correlated with impaired performance on the color-word Stroop task.[36] The difference between these two studies suggests that the changes are not robust, however, and that further study is needed.

Functional Connectivity

Functional Connectivity at a Resting State:

Early studies in participants with IGD showed increased functional connectivity among regions of the brain that are associated with cognitive regulation, signal processing, and storage of relevant auditory-verbal memory processes.[37] These findings are consistent with current models of the role of cortical-subcortical pathology in addiction.[38] Disruption of functional connectivity in IGD may also affect motivation and reward. For example, smokers with IGD have exhibited decreased functional connectivity among brain regions involved in the evaluation and expectation of reward.[39] Study participants with IGD showed reduced connectivity in areas responsible for executive function and increased connectivity within sensory-motor brain networks.[40] Reduced functional connectivity in IGD affected executive control networks.[41] These participants also showed an increase in caudate and nucleus accumbens volume, as well as reduced resting-state functional connectivity between the *dorsal prefrontal cortex* (DPFC) segment of the caudate, OFC, and nucleus accumbens—regions associated with reward.[42] Impulsivity was also shown to have a negative correlation with functional connectivity among the amygdala, DPFC, and the OFC[43] and was associated with alterations in frontal-limbic connections.[44]

Summary: These are few studies with several brain regions that have been specifically related to drug addiction but they also mention other regions that are associated with general cognitive function. Therefore, more studies need to be conducted in order to select related from unrelated brain regions.

Recent Studies in Adolescents:

Consistent with recent models of the role of cortical-subcortical pathology in addiction, adolescents with IGD showed reduced functional connectivity in cortical-subcortical circuits.[45] They have also demonstrated a disruption in functional connectivity in areas responsible for learning, memory, and executive function, as well as in the processing of auditory, visual, and somatosensory stimuli and in the relay of sensory and motor signals.[46] Adolescents with IGD have demonstrated a decrease in functional connectivity within the *prefrontal cortex* (PFC) and striatal circuits areas associated with reward.[47] They have also shown reduced dorsal putamen functional connectivity with the posterior insula-parietal operculum[48] and an increase in grey matter volume in the dorsal striatum (caudate) and the ventral striatum (nucleus accumbens)[49] in the presence of enhanced resting-state functional connectivity between the anterior insula and areas involved in salience, craving, self-monitoring, and attention.[50] Participants with IGD also had stronger functional connectivity between the left posterior insula and other brain regions associated with a reduced ability to inhibit motor responses and control their craving for internet gaming.[50] Connectivity between parts of the frontal cortex was also reduced.[51] Finally, adolescents with IGD demonstrated increased functional connectivity in brain regions involved in working memory, spatial orientation, and attention processing.[52]

Summary: Connectivity in several areas of the brain that are responsible for executive function, cognitive control, sensory processing motivation, and reward was reduced in participants with IGD. Connectivity among some of these regions is common to IGD and substance use disorders, but connectivity among other areas is associated with general mechanisms of learning, memory, and information processing that are not specific to IGD and substance use disorder. No inferences on causality can be drawn based on any of the studies carried out thus far. A better selection of subjects is required for future studies. See Table 2 for a summary of studies of functional connectivity in IGD.

Table 2:
Studies of Functional Connectivity in fMRI[1]

Main Findings and Evaluation	Participants	Method	Citation
Increased functional connectivity in the bilateral posterior lobe of cerebellum and middle temporal gyrus Decreased connectivity in bilateral inferior parietal lobule and right inferior temporal gyrus Connectivity with PCC correlated with internet addiction scores in the right precuneus, PCC, thalamus, caudate, nucleus accumbens, SMA, and lingual gyrus Connectivity with PCC correlated negatively with right cerebellum, anterior lobe, and left SPL.	Adolescents with IGD (n = 17) Controls (n = 24)	Functional connectivity in fMRI	Ding et al., 2013
Reduced functional connectivity in cortical-subcortical circuits .~24% with pre-frontal and ~27% with parietal cortex) Bilateral putamen was the most extensively involved subcortical brain region.	Adolescents with IAD (n = 12) Controls (n = 11)	Functional connectivity in fMRI	Hong et al., 2013
Higher global CBF in left inferior temporal lobe/fusiform gyrus, left PHG/amygdala, right medial frontal lobe/ACC, left and right insula, right middle temporal gyrus, right precentral gyrus, left SMA, left cingulate gyrus, and right inferior parietal lobe Lower CBF in left middle temporal gyrus, left middle occipital gyrus, and right cingulate gyrus	Adolescents with IGA (n = 11) Age-matched controls (n = 18)	ASL perfusion in fMRI	Feng et al., 2013
Disruption in the functional connectivity with the frontal, occipital, and parietal lobes Functional connectivity within any lobe correlated with the IAD severity	Adolescents with IGD (n = 17) Controls (n = 16)	Functional connectivity in fMRI	Wee et al., 2014
Decreased resting state functional connectivity with posterior cingulate cortex in the right rectus gyrus Increased resting state functional connectivity with the left middle frontal gyrus in smokers with IGA compared with nonsmokers with IGA	Smokers with IGD (n = 29) Nonsmokers with IGD (n = 22) Controls (n = 30)	Functional connectivity in fMRI	Chen et al., 2014
Lower functional connectivity in executive control networks Negative correlation between functional connectivity measures in executive control networks and Stroop effect Positive correlation between brain activation and executive control regions across groups	IGD (n = 35) Controls (n = 36)	Functional connectivity in fMRI	Dong et al., 2015
Lower GMD in the bilateral amygdala and higher impulsivity Lower functional connectivity with the left amygdala over the left DLPFC and with the right amygdala over the left DLPFC and OFC Higher functional connectivity with the bilateral amygdala over the contralateral insula Negative correlation between functional connectivity between the left amygdala and DLPFC vs impulsivity Negative correlation between functional connectivity between right amygdala and left DLPFC and OFC vs impulsivity.	IGD (n = 30 males) Controls (n = 30)	GM density and functional connectivity in fMRI	Ko et al., 2015

Main Findings and Evaluation	Participants	Method	Citation
Reduced dorsal putamen functional connectivity with the posterior insula-parietal operculum Time spent playing online games predicted significantly greater functional connectivity between dorsal putamen and bilateral primary somatosensory cortices Lower functional connectivity between the dorsal putamen and bilateral sensorimotor cortices in healthy control participants	Adolescents with IGD (n = 12 males) Controls (n = 11)	Functional connectivity in fMRI in subdivisions of striatum	Hong et al., 2015
Decreased VMHC between left and right superior frontal gyrus (orbital part), inferior frontal gyrus (orbital part), middle frontal gyrus, and superior frontal gyrus	IGD (n = 17) Healthy controls (n = 24)	Functional connectivity and VMHC method	Wang et al., 2015
Enhanced functional connectivity between the anterior insula and a network of regions that includes the ACC, putamen, angular gyrus, and precuneous Stronger functional connectivity between the posterior insula and postcentral gyrus, precentral gyrus, SMA, STG Positive relationship between IGD severity and connectivity between the anterior insula and AG, STG, and with connectivity between the posterior insula and STG Positive relationship between duration of internet gaming and connectivity between the anterior insula and ACC	Young adults with IGD (n = 74) Controls (n = 41)	Functional connectivity of the insula in fMRI	Zhang et al., 2015
Increased volume of dorsal striatum (caudate) and ventral striatum (nucleus accumbens), with more errors on the Stroop task Caudate volume correlated with Stroop task performance and NAc NAc volume was associated with IAT score in the IGD group	Adolescents with IGD (n = 27) Controls (n = 30)	Functional connectivity in fMRI in striatal nuclei (caudate, putamen, and nucleus accumbens) volumes	Cai et al., 2016
IGD adolescents exhibited higher global/long-range rsFCD in the bilateral DLPFC and the right ITC/fusiform compared with healthy control participants	Adolescents with IGD (n = 27 males) Healthy controls (n = 35)	rsFCD in fMRI	Du et al., 2016
Decreased functional connectivity between the insula and the temporal and occipital cortices and dorsal striatum, pallidum, and thalamus in IGD Some of those changes were associated with the severity of IGD.	Adolescents with IGD (n = 25) Gender-matched controls (n = 25)	Functional connectivity	Jin et al., 2016
Reduced connectivity in the prefrontal cortex, left posterior cingulate cortex, right amygdala, and bilateral lingual gyrus Increased functional connectivity in sensory-motor-related brain networks in IGD	IGD (n = 37) Matched controls (n = 35)	Functional connectivity	Wang et al., 2016
Enhanced functional connectivity between the anterior insula and the ACC, putamen, angular gyrus, and precuneous Stronger functional connectivity between the posterior insula and postcentral gyrus, precentral gyrus, supplemental motor area, and superior temporal gyrus (STG). IGD severity was positively associated with connectivity between the anterior insula and angular gyrus, and STG, and with connectivity between the posterior insula and STG Duration of internet gaming was positively associated with connectivity between the anterior insula and ACC	Young adults with IGD (n=74) Age- and gender-matched controls (n = 41)	Functional connectivity of insula-based network	Zhang et al., 2016
Enhanced functional connectivity in the bilateral DLPFC and the right ITC/fusiform	Adolescents with IGD (n = 27 males) Controls (n=35)	Functional connectivity	Du et al., 2016

Main Findings and Evaluation	Participants	Method	Citation
Higher impulsiveness and higher global efficiency and lower local efficiency in pathological states Topological alterations specifically attributable to interregional connections incident on the frontal region Degree of impulsiveness was associated with the topological alterations over the frontal-limbic connections	Adolescents with IGD (n = 19) Age-matched controls (n = 20)	Functional connectivity in fMRI	Park et al., 2017
Reduced FA in salience network, right central executive network tracts, and between-network (ACC-right DLPFC tracts) Correlation between the effective and structural connection between salience network and central executive network vs the number of errors made during incongruent condition in Stroop task	Adolescents with IGD (n = 28) Controls (n = 25)	Functional connectivity in fMRI	Yuan et al., 2017

[1] Studies arranged chronologically
ACC, anterior cingulate cortex
AG, angular gyrus
ASL, arterial spin-labeling
CBF, cerebral blood flow
DLPFC, dorsolateral prefrontal cortex
GMD, grey matter density
IAD, internet addiction disorder
IAT, internet addiction test
MPFC, medial prefrontal cortex
NAc, nucleus accumbens
OFC, orbitofrontal cortex
PCC, posterior cingulate cortex
PET, positron emission tomography
PHG, parahippocampal gyrus
PLIC, posterior limb of the internal capsule
rCMRglu, regional cerebral metabolic rates of glucose
rsFCD, functional connectivity density
SMA, supplementary motor area
SPL, superior parietal lobule
STG, superior temporal gyrus
VMHC, voxel-mirrored homotopic connectivity

Brain Activation

Cue-Exposure Activation Studies of Video Game Urges:

Males with IGD demonstrated greater activation in the mesocorticolimbic system compared with females while playing a space infringement game.[53] fMRI studies showed that several frontal, striatal, and limbic regions were activated in these participants.[54] A longitudinal fMRI study of cue reactivity found activation in the ACC and OFC in these participants over 6 weeks.[55] Gaming cues also activated regions that are associated with the urge to play games.[56] Furthermore, gaming and smoking cues shared similar mechanisms of cue-induced reactivity in the frontal limbic network.[57] Exposure to World of Warcraft game figures activated brain regions associated with cognitive and emotion- and motivation-related functions.[58] Activation of regions associated with visuospatial orientation, space, attention, mental imagery, and executive function was enhanced,[59] as was attention to short presentations of game pictures and responses in the medial PFC and the ACC.[60] Activation of areas associated with visuospatial attention and body self-awareness was observed in adolescents with IGD during ball-throwing animations simulating the experience of a "disembodied state" in cyberspace.[61-62]

Summary: A consistent pattern of activation in response to stimulation with video playing was observed in specific brain regions in IGD. Studies using tasks that simulate reward[15] allowed investigators to assess the effects of cue exposure on the brain. Thus far, however, only one brain-imaging study[55] has followed cue activation over time to allow investigators to assess causality.

Recent Activation Studies in IGD:

IGD participants exhibited higher cue-induced activation within the ventral and dorsal striatum compared with healthy controls.[63] Activation of the dorsal striatum correlated with the duration of IGD, indicating a transition from ventral to dorsal striatal processing.[61] Internet gaming addiction appears to be associated with an increased identification with one's imaginary virtual person ("avatar"), as indicated by strong activation of the left angular gyrus in pathological internet gamers.[64] The result of this experimental manipulation suggests how self-identification during video game playing can affect brain mechanisms responsible for processing auditory, visual, and somatosensory modalities. Addiction to social networks was characterized by emotion regulation deficits reflected in reduced striatal activation during self-reflection compared with ideal reflection in IGD players.[64] This experimental manipulation of self-reflection is related to brain activation and may indicate how the two interact.

Summary: Several studies have shown a consistent pattern of brain activation in response to video game playing stimuli that is similar to the activation associated with drug cues. Regions consistently activated by cue exposure were the caudate nucleus, OFC, DLPC, *inferior*

frontal cortex (IFC), ACC, PCC, parahippocampus, and precuneus.[12] In a single study,[63] investigators found an association between parts of the striatum and the duration of IGD, indicating long-term changes as a result of play. These studies show how cue exposure can affect the brain's reward system and processing of sensory information, as well as self-reflection.

Inhibitory Control Mechanisms:

Individuals with IGD display faulty inhibitory control mechanisms, such as impaired response-inhibition on the Stroop task and related activity in the ACC and PCC.[65] They have also made more commission errors on go/no-go tasks and demonstrated impaired response inhibition during gaming cue distractions.[66] Impulsivity and response inhibition were associated with impaired function in the insula and greater activation of the frontal striatal network.[67] IGD participants also showed greater impulsivity and lower motor area activation while performing the go/no-go task.[68] Adolescents with IGD exhibited increased activity in attention and motor areas during these trials.[69] IGD participants failed to recruit frontal basal ganglia pathways and inhibit unwanted actions on the go-stop paradigm.[70] They also demonstrated higher activation in brain areas that are involved in selective attention, visual processing, working memory, and cognitive control while processing internet gaming-related stimuli on a modified Stroop task.[71] In a recent study of individuals with IGD, investigators found decreased left middle and superior temporal gyrus activation during interference of socially anxious words, which may indicate social anxiety.[72] A meta-analysis concluded that individuals with IGD are more likely to exhibit impaired response inhibition.[73]

Summary: Impaired performance of response inhibition tasks is consistently followed by failure to recruit frontal basal ganglia pathways and use of other brain areas during inhibition in both adolescents and adults with IGD.

Reward:

IGD is associated with faulty decision-making and a preference for immediate rewards versus long-term gains. Individuals with IGD subjectively experienced monetary gain and loss during the performance of a guessing task.[74] They also showed increased activation in the OFC in gain trials and decreased activation in the ACC during loss trials; this suggests enhanced sensitivity to rewards and decreased sensitivity to loss. During an fMRI study, participants with IGD also showed increased activity in the IFC, insula, and ACC and decreased activation in the caudate and PCC after continuous wins during the performance of a continuous wins-and-losses task.[75] fMRI studies also showed that IGD participants prefer probabilistic options over fixed ones and responded faster during a probability-discounting task compared with controls.[76] They also showed decreased activation in the inferior frontal gyrus and precentral gyrus while the participant selected probabilistic options compared with controls. These participants selected risk-disadvantageous choices and made risky decisions more hastily and with recruitment of fewer regions governing impulse control.[77] Adolescents with IGD exhibited decreased sensitivity to rewards and were only sensitive to error monitoring regardless of positive feelings, such as sense of satisfaction.[78] These findings suggest impaired decision-making, together with enhanced activation of compensatory brain mechanisms governing impulsive decision-making. In a recent study, investigators found that negative outcomes affected the covariance between risk level and activation of brain regions governing value estimation (PFC), anticipation of rewards (ventral striatum), and emotion-related learning (hippocampus), which may be one of the underlying neural mechanisms of disadvantageous risky decision-making.[79] IGD participants exhibited stronger functional connectivity when selecting small and immediate gains during a delay-discounting task.[80] These results indicate that IGD participants have enhanced sensitivity to rewards and a decreased ability to control their impulsivity effectively, which leads to suboptimal decision-making.[80] Males with IGD showed decision-making deficits indicating an imbalance between hypersensitivity for reward and weaker risk experience and self-control for loss.[81] A recent review has suggested that both patients with IGD and pathological gamblers exhibit decreased loss sensitivity, enhanced reactivity to gaming and gambling cues, enhanced impulsive choice behavior, aberrant reward-based learning, and no changes in cognitive flexibility.[82]

Summary: Adolescents with IGD exhibit increased risk-taking choices and an impaired ability to control

their impulses, similar to individuals with other impulse control disorders. These characteristics were detected using simulated decision-making tasks to assess the effects of faulty decision-making processes on brain mechanisms responsible for reward.

Brain Imaging Studies of Dopamine and 5-HT in Comorbid Psychiatric Disorders

Neurotransmitters such as dopamine and serotonin (5-HT) play important roles in drug and alcohol dependence, mainly by mediating DA reward and withdrawal mechanisms.[83-84] Consistent with evidence that drug use disorders and AUDs are associated with dopamine-deficient reward activity,[85-88] **IGD participants showed reduced availability of dopamine (D_2) receptors[89] and *dopamine transporters* (DATs) in the striatum.**[90] Finally, male IGD participants showed a significant decrease in glucose metabolism in the prefrontal, temporal, and limbic regions of the brain and reduced D_2 receptor availability in the striatum.[91] This suggests that D_2 receptor-mediated dysregulation of the OFC may underlie a mechanism for loss of control and compulsive behavior in IGD. Because there is no baseline measure of dopamine levels before addiction sets in, it is not possible to determine whether dopamine deficiency is a predisposing factor for drug use disorders and AUDs or IGD. Magnetic resonance spectroscopy studies have shown lower levels of N-acetyl aspartate in the right frontal cortex and choline in the medial temporal cortex in participants with IGD that are similar to those seen in patients with *attention-deficit/hyperactivity disorder* (ADHD) and clinical depression.[92] Evidence provided thus far supports the hypothesis that deficient dopaminergic reward activity can be used to classify IGD as a behavioral addiction. The association between IGD and impaired self-regulation is also compatible with the model of IGD as an impulse control disorder within the impulsive-compulsive spectrum.[1] In a recent study, individuals with IGD showed altered PCC functional connectivity that might be associated with a history of childhood ADHD.[93] These findings suggest that altered neural networks for executive control in ADHD may predispose the patient to develop IGD. In another study using qualitative EEG to compare adolescents with IGD with or without ADHD, adolescents who showed greater vulnerability to ADHD seemed to play internet games continuously to enhance their attention skills.[94] Repetitive activation of brain reward and working memory systems during continuous gaming may result in an increase in neuronal connectivity within the parietal, occipital, and temporal regions in participants with comorbid ADHD and IGD.[94] Finally, investigators found that hippocampal activity during an attention-demanding task was not suppressed in participants with comorbid IGD and major depressive disorder who took the *Wisconsin Card Sorting Task*. This may have been a consequence of depression.[95] Patients with IGD have also shown increased functional connectivity among several executive control brain regions that may be related to psychiatric comorbidity with ADHD and depression.[96] In a qualitative EEG study, comorbidity of IGD and MDD was also indicated by decreased interhemispheric connectivity in the frontal region and vulnerability to attention problems.[97] Furthermore, increased intrahemispheric connectivity within any lobe of the brain may arise as a result of excessive online gaming. Comorbidity of depression and ADHD may also be associated with dopamine deficiency in IGD. Further studies are needed to investigate the similarity in neurochemical and neurocognitive brain circuits in IGD and its comorbid conditions.

Discussion

The findings of studies reviewed so far consistently demonstrate the resemblance between neural mechanisms underlying substance use disorders and those underlying IGD. In accordance with the behavioral addiction model, IGD demonstrates features of excessive use despite adverse consequences, withdrawal phenomena, and tolerance that characterize substance use disorders. Support for the behavioral addiction model of IGD is provided by structural and functional changes in the mechanisms of reward and craving (but not withdrawal). A recent meta-analysis revealed significant activation of brain regions that mediate reward (the bilateral medial frontal gyrus and left cingulate gyrus) in participants with IGD.[98] These studies support the notion that IGD is associated with changes in the brain's reward system and mechanisms of loss of control and inhibition. There is also longitudinal evidence that treatment with medications such as bupropion can

attenuate cue reactivity in IGD[99] in a manner similar to that seen in nicotine-dependent individuals.[100] IGD is associated with a reduction in dopamine transporter density and dopamine D_2 receptor occupancy in the brain. Excessive use of the dopamine reward system results in a down-regulation resembling that seen in drug and alcohol abuse, although in both disorders there are no baseline measures prior to the addiction precluding any inferences about causality. Finally, there is pharmacogenetic evidence that dopaminergic genes (Taq1A1 variation of the D_2 receptor and low-activity Val158Met in catecholamine-o-methyltransferase alleles)[101] and serotonergic genes (SS-5HTTLPR), together with personality factors, may play a role in vulnerability to IGD.[102] Evidence for genetic dopaminergic vulnerability is compatible with the behavioral addiction model of IGD; consequently, IGD may be classified as a reward deficiency syndrome.[103-104] Evidence of genetic serotonergic vulnerability and brain imaging studies support the comorbidity of IGD, anxiety-related OCD, and depression. Finally, playing games may be actually good for you—recent studies have shown that playing computer games could improve plasticity in the brain and, thus, be advantageous in such conditions as posttraumatic stress disorder, schizophrenia, and neurodegenerative disease.[105]

One of the major limitations in brain imaging studies of IGD is that they are mainly cross-sectional studies without baseline measures and rely on associations between structural and functional changes in the brain and in internet and video game characteristics. These associations do not provide any proof that IGD activity plays a causal role in the development of the adolescent or adult brain. There are factors that may mediate such associations, such as educational, cognitive, emotional, and social factors. There are methodological considerations of age (use by adolescents and students), culture (most studies were done in the Far East), and lack of comparison with substance use disorder groups. These are major limitations of the studies that have been reviewed so far. Finally, very few studies looked at sex differences in cognitive and brain function in IGD.

Summary

There is emerging evidence that IGD is associated with brain mechanisms similar to those responsible for substance use disorders. Brain imaging studies in IGD have shown similarities in brain mechanisms involved in IGD and substance use disorder and, therefore, support the classification of IGD as a behavioral addiction.

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Multiple-Choice Questions

33. According to the lesson, excessive internet gaming was associated with abnormal resting state activity in brain regions that are responsible for:

A. Impulse control.

B. Reward processing.

C. Somatic representations of previous experiences.

D. All of the above.

34. IGD participants had lower gray matter density in brain regions that are involved in which of the following?

A. Decision making

B. Behavioral inhibition

C. Emotional regulation

D. All of the above

35. In males, what is the main area that has been activated in cue-exposure studies of video game playing?

A. Mesocortical reward system

B. Motor function

C. Visual perception

D. All of the above

36. Which neurotransmitter has been consistently shown to be deficient in IGD?

A. Dopamine

B. Serotonin (5-HT)

C. Acetylcholine

D. Norepinephrine

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Best Practices in CME

Internet and Gaming Disorder and Associated Changes in the Brain

By Aviv Weinstein, PhD

ID#: L003412

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key 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, pediatricians, and family physicians who are interested in current information about *internet gaming disorder* (IGD). Knowing the effects of IGD on the brain can only increase our ability to identify and better understand this disorder.

Key Point 1: Diagnosis and Models of IGD

There are different models of IGD. It has been argued that IGD fits the behavioral addiction model because it is characterized by excessive use despite adverse consequences, withdrawal phenomena, and tolerance, which characterize substance use disorders. Some have suggested that it fits the model of an impulse control disorder or part of the obsessive-compulsive disorder (OCD).

Key Point 2: Brain Imaging Studies of the Resting State in IGD

Excessive internet game use has been associated with abnormal resting state activity in the brain regions that are responsible for impulse control, reward processing, and somatic representation of previous experiences.

Key Point 3: Structural Studies of the Brain's Gray Matter Volume and White Matter Density in IGD

There is evidence of changes in gray matter volume and white matter density in IGD. A few studies have shown that changes in white matter density in several regions of the brain may affect neural transmission.

Key Point 4: Increased Functional Connectivity in IGD

Early studies in participants with IGD showed increased functional connectivity among regions of the brain that are associated with cognitive regulation, signal processing, and storage of relevant auditory-verbal memory processes.

Key Point 5: Activation Studies in IGD

Studies have shown that brain reward mechanisms are activated in response to video-playing stimuli in IGD. IGD has also been associated with faulty decision making and loss of control.

Key Point 6: Interaction of Brain Neurotransmitters and Comorbidity with IGD

Consistent with evidence that drug and alcohol use disorders are associated with deficient dopamine reward activity, studies have shown that dopamine levels may be reduced in individuals with IGD. Evidence of genetic serotonergic vulnerability, coupled with brain imaging studies, support the comorbidity of IGD with anxiety OCD and depression.

Notes

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Vitamins, Minerals, and Herbs: Their Effects on Neurocognitive Disorders

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No commercial support was used in the development of this CME lesson.
The vitamins and herbs mentioned herein are not approved by the FDA for the treatment of neurocognitive disorders in the USA.

KEY WORDS: Vitamins • Herbs • Neurocognitive disorders

LEARNING OBJECTIVES: On completing this lesson, the clinician will be able to (1) describe *neurocognitive disorders* (NCDs) and identify their neurocognitive domains; (2) identify the clinical characteristics of *Alzheimer's disease* (AD) and explain current theories about its pathophysiology; and (3) explain the potential effects of vitamins, minerals, and herbs on cognition.

LESSON ABSTRACT: Given the increasing impact of NCDs on the family, the community, and the economy as the population increases in age, there has been a heightened focus on the use of supplements to promote health. To help clinicians make the most useful recommendations for their patients, we present a review of renamed and new categories of major and minor NCDs that appear in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders,* with a focus on AD (the most common form of dementia), and present an assessment of specific vitamins, minerals, and herbs that have been suggested to improve cognition or slow cognitive decline.

COMPETENCY AREAS: This lesson provides knowledge on a subject that is not frequently discussed in patient care, particularly for patients with deficiencies in cognition. On completing this lesson, the reader will be able to discuss current definitions of major and minor NCDs, particularly AD, and the effects of vitamins, minerals, and herbs on cognition.

Introduction

Neurocognitive disorders (NCDs) are characterized by impairment of the ability of the individual to acquire information and knowledge and understand and acts in the world. According to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*),[1] NCDs include delirium, as well as syndromes of major NCDs and mild NCDs and their subtypes. Despite the significant overlap of cognitive deficits with many mental disorders, a diagnosis of an NCD is made only when the core features include a deficit in cognition and a decline in cognition.[1]

When patients present with memory problems or changes in behavior, the physician's initial dilemma is to determine whether these cognitive changes are clinically relevant. A major NCD is characterized by impairment in one or more cognitive domains (Table 1) that is severe enough to interfere with *activities of daily living* (ADLs) and results in the patient requiring assistance. A mild NCD is characterized by a decline in cognitive functioning does not interfere with the ability of the patient to carry out ADLs independently. In neither case should the cognitive deficits be the result of delirium or accounted for better by another mental disorder (e.g., major depressive disorder, schizoaffective disorder, or schizophrenia). After a cognitive deficit has been confirmed, its etiology must be determined. These include Alzheimer's disease; Parkinson's disease; Huntington's disease; *traumatic brain injury* (TBI), vascular; Lewy bodies, frontotemporal disorders; HIV; prion disease, substance/medication-induced; or another medical condition (multiple and unspecified).

Table 1:
Neurocognitive Domains

Complex attention	Sustained attention, divided attention, selective attention, processing speed
Executive function	Planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility
Learning and memory	Immediate memory, recent memory, very-long-term memory
Language	Expressive language and receptive language
Perceptual-Motor	Visual perception, visuoconstructional, perceptual-motor, praxis, and gnosis
Social cognition	Recognition of emotions, theory of mind

Adapted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Arlington, VA: American Psychiatric Association; 2013.

NCDs, particularly major NCDs, have a significant impact on the individual, family, and community, as well as the economy. It is estimated that more than 35 million people worldwide had dementia in 2010, and it has been predicted that this number will double every 29 years.[2] In the United States, AD remains the sixth leading cause of death.[3] Increasing age is the strongest risk factor for dementia.[4] AD represents approximately 60% to more than 90% of all cases of dementia.[1] With life expectancy increasing, there is a heightened focus on ways to preserve cognition and promote healthier lifestyles.

Vitamins have been shown to reduce both the incidence and progression of many neurological diseases, particularly AD.[1] Interest in the use of vitamin and herbal supplements in AD is growing as a result of the findings of a limited number of studies suggesting that some vitamins and herbs can help preserve cognition.

We will review the clinical characteristics of AD and some current theories about its pathophysiology. A summary of over-the-counter supplements that have been touted to improve cognition is also provided, as well as a discussion of their potential benefit and risks.

Alzheimer's Disease

AD is one of the most common forms of dementia in the United States. Characterized by marked impairment in cognition and behavior, it is an incurable progressive condition with a long preclinical period. In 2017, approximately 6 million Americans had been diagnosed with clinical or *mild cognitive impairment* (MCI) due to AD; this number is expected to rise to 15 million by 2060. AD is currently the sixth leading cause of death in the United States.[5]

To understand the nature of AD, we need to understand the nature of neuronal activity. Healthy neurons have support systems consisting of microtubules, which act as intracellular tracks guiding nutrients from the cell body toward the axon terminal and back again. The protein tau binds to these microtubules to stabilize them. In AD, a chemical change takes place in the structure of tau that causes it to bind to other tau threads, which results in the formation of *neurofibrillary tangles* (NFTs). This causes the microtubules to collapse, which leads to cell death. NFTs are found primarily in the temporal lobe and affect the hippocampus most severely.[6] As AD progresses,

NFTs accumulate in many other cortical regions, beginning with high-order association regions and occurring less frequently in the primary motor and sensory regions.

There is a significant overlap in the pathophysiology of normal aging and the progression of AD. This was demonstrated in a study in which neuropathologists who were blinded to clinical data identified 76% of brains obtained postmortem from cognitively intact elderly patients as exhibiting AD.[7] Multiple theories have been proposed to explain the pathophysiology of progression toward AD. One main theory proposes a role for the damage caused by oxidative stress and consequent inflammatory reactions. Multiple studies have shown that oxidative damage primarily affects areas that regulate cognitive performance. Intracellular responses to oxidative stress cause changes in mitochondria and other organelles (most notably the endoplasmic reticulum) that can result in cell death in a number of ways (e.g., necrosis, apoptosis).[8] The formation of free carbonyls and thiobarbituric acid-reactive products (which serve as an index of oxidative damage) is significantly increased in the brain tissue of individuals with AD compared with age-matched controls.

Oxidative stress causes alterations in the cell structure in a number of ways. For example, it can result in the formation of *reactive oxygen species* (ROS) within the cell membrane and damage the integrity of the membrane. This can result in disturbances in ion homeostasis that can result in an increase in intracellular levels of calcium. It can also increase the rate of the accumulation of ROS, which can damage a number of intracellular components (e.g., proteins, lipids, mitochondria, and DNA) and result in apoptotic cell death. A concurrent decrease or lack of antioxidant mechanisms can aggravate the results of oxidative stress in AD. For example, glutathione—an antioxidant that helps confer protection against the effects of free radicals—appears in reduced levels in patients with AD.[9,10]

Another important factor in the development of AD is the development of senile plaques, which are dense insoluble deposits of protein and cellular material that surround the outer surface of neurons. Plaques usually consist of beta amyloid, a protein cut off from a larger protein called amyloid precursor protein. In AD, these plaques form in the hippocampus, which plays a key role in the formation of memory, and in other areas of the brain that are involved in thinking and decision making.[11]

These three theories are interrelated. ROS leads to the oxidation of proteins, which leads to protein aggregation and the dimerization that results in the structurally abnormal proteins found in tau tangles and beta amyloid plaques. Increased levels of beta amyloids cause oxidative stress,[12] primarily because of methionine, a toxic component of beta amyloid that is implicated in multiple oxidative processes.[13]

Thus, both an increase in oxidative stress and decrease in anti-ROS intracellular defense mechanisms contribute to the pathogenesis of AD.

As potent antioxidants, vitamins have shown considerable promise in the ability to reduce oxidative stress and neuronal damage in neurocognitive disorders.

The Role of Vitamins in Cognition

Vitamin A and Beta Carotenes:

Studies have shown that vitamin A and beta carotene levels in serum, plasma, and *cerebrospinal fluid* (CSF) are notably low in patients with AD compared with controls.[14] These vitamins have important roles in multiple aspects of neurodegenerative disorders. Vitamin A has a very pivotal role in the early development of neurons that continues into the late stages of adult life. **Vitamin A assists in the regeneration of degenerating neurons and protects healthy neurons against degeneration.**[15] Specifically, vitamin A has been shown to decrease the oligomerization of beta amyloid protein fibrils to stop them from aggregating.[16] Because vitamin A is fat-soluble, excess amounts can accumulate in the liver and cause significant toxicity.

Beta carotenes are lipid-soluble antioxidants that may reduce lipid peroxidation, improve antioxidant status, and scavenge singlet oxygen moieties rapidly.[17,18] These are exogenous chain-breaking antioxidants that reduce the number of toxic chain reactions in neuronal cells that produce cytotoxic free radicals.[19] Beta carotenes are also associated with the anti-oligomerization of beta amyloid proteins.[15] At relatively high plasma levels, they have been associated with better performance on memory tests.[20]

Thus, both vitamin A and beta carotene have been shown to slow the decline of cognition in AD patients.

B Vitamins:

The B vitamins associated with the prevention of memory decline include thiamine (vitamin B1), niacin (vitamin B3), pyridoxine (vitamin B6), folic acid (vitamin B9), and cobalamin (vitamin B12). Niacin has also been shown to protect against age-related cognitive decline and AD.[21] Cobalamin deficiency has also been linked to a neurological syndrome that is characterized by both cognitive and psychological disturbances and subacute degeneration of the spinal cord and peripheral neuropathy.[22,23] It is now standard procedure to rule out cobalamin deficiency before making a diagnosis of AD.

Pyridoxine, cobalamin, and folic acid have been shown to be very important in the management of AD primarily through their effects on homocysteine, an amino acid that is thought to increase neuronal toxicity by triggering the formation of ROS, thereby increasing oxidative stress. Homocysteine affects brain function through its effects on the vasculature of the brain as well as its neurotoxic effects.[24] Hyperhomocysteinemia is an isolated yet important risk factor in the development of AD. **Pyridoxine, folic acid, and cobalamin increase the metabolism of homocysteine, thereby reducing its levels in the blood and its ability to induce oxidative stress**.[25]

Low levels of pyridoxine contribute to the pathogenesis of AD and development of white matter lesions in the brain.[26] Low folate levels may also predict the development of AD. In a study of 816 participants, investigators found a statistically significant relationship between low folate levels and AD.[27] A lack of folate allows homocysteine levels to rise; this may contribute to impaired calcium influx, which can lead to cell death, the accumulation of tau tangles, and the formation of beta amyloid proteins. Folate deficiency has also been associated with significant atrophy of the cerebral cortex.[28] This effect was evaluated in a 10-year study of a large cohort of 1351 of individuals over the age of 65 years from France—where none of the foods are fortified with folic acid and intake of this vitamin is relatively low. In this study, investigators found a strong relationship between a higher intake of folate and a lower incidence of long-term complications of dementia.[29] In another study, investigators found that supplementation of the diet with a combination of folic acid, pyridoxine, and cobalamin can slow the rate of atrophy in brain regions associated with cognition.[30]

Vitamin C:

Vitamin C increases serum levels of superoxide dismutase, which helps reduce oxidative stress.[31] It can slow the progression of AD by altering the rate of oligomerization of beta amyloid peptides. Serum levels of this vitamin have been shown to be lower in patients with AD despite an adequate dietary intake.[32]

Vitamin D:

Vitamin D functions as an antioxidant, affects calcium regulation in nerves, has immune-modulating properties, enhances nerve conduction, and can detoxify nerves. It may be involved in the clearance of amyloid-beta peptides and the phosphorylation of tau peptides. Thus, it may provide some protection against neurodegenerative mechanisms that are associated with AD. The active form of vitamin D is important for brain development and, therefore, vital for normal adult brain function. The areas of the brain that are involved in complex functions, processing, and memory formation have vitamin D receptors, which suggests an important role for this vitamin in neurocognitive functioning.[33,34] Elderly patients are at higher risk for vitamin D deficiency because of reduced production of this vitamin in the skin and a lower dietary intake compared with younger cohorts.[35] As of this writing, no randomized placebo-controlled trials have been conducted to examine the therapeutic benefit of vitamin D supplementation in the prevention of AD. Several nonrandomized controlled studies in older adults have shown cognitive improvement after 1 to 15 months of vitamin D supplementation.[36-37] A 2012 systematic review and meta-analysis of the relationship between cognitive function/dementia and vitamin D levels in adults associated lower vitamin D levels with worse cognitive function and a higher risk for AD.[38]

Vitamin E:

Vitamin E consists of eight antioxidants in total: four tocotrienols and four tocopherols. This vitamin acts as a scavenger for free radicals[39] and helps in the regeneration of superoxide dismutase, which reduces oxidative stress. A deficiency leads to early destruction of neurons due to

the inability to initiate their repair. Furthermore, vitamin E levels have been found to be lower in patients with AD. **Nevertheless, a 2017 Cochrane Review found no evidence that vitamin E supplementation can prevent progression to dementia or improve cognitive function in patients with MCI or AD.**[40]

The Role of Minerals in Cognition

Iron:

Iron deficiency is the most prevalent nutritional deficiency worldwide and, along with anemia, affects women and children disproportionately. Anemia is used as a surrogate term for iron deficiency worldwide, even though iron deficiency can exist without the manifestation of anemia. Thus, iron deficiency is likely to be underestimated. It is well recognized that perinatal iron deficiency affects neurocognitive development and that iron supplementation prevents neurocognitive decline. Iron deficiency affects the hippocampus, where it causes recall memory problems, and the prefrontal cortex, where it affects executive functions such as planning or inhibitory control. A delay in the correction of iron deficiency can have a lasting effect on neurocognition in young children, even after the deficit has been corrected.[41,42] Iron supplementation may also be associated with health risks. While there has been no known direct correlation between iron levels and cognitive decline in the elderly, **there is a concern that excess iron in the brain may increase oxidation and the risk for dementia.**

Zinc:

Zinc deficiency or excess cannot be detected early using current laboratory techniques. As a micronutrient, zinc has a narrow therapeutic index. An excess may cause considerable toxicity. A deficiency may have a dramatic effect on neurocognitive development of the fetus. Zinc supplementation remains a promising area of research. Translational research into the development of better tests to detect zinc levels accurately is needed before a final recommendation can be made.[43, 44]

Magnesium:

Elevated levels of magnesium in brain tissue have been shown to have a substantial protective effect on synapses in a mouse model of AD and in patients with TBI. As a result, it is been postulated that elevated magnesium levels in the brain have therapeutic potential in these two conditions. There is no definitive evidence that magnesium supplements will improve neurocognitive function, however.[45]

Acetyl-L Carnitine:

L-carnitine and its acetylated derivative *acetyl-l-carnitine* (ALCAR) have been studied in a number of disorders, including TBI, AD, and conditions leading to central nervous system injury. Preclinical studies in models of adult, neonatal, and pediatric brain injury suggest that l-carnitine and ALCAR can improve energy status, decrease oxidative stress, and prevent subsequent cell death. Its mechanism of action is thought to involve the incorporation of glutamate, glutamine, and gamma-aminobutyric acid into lipids to support myelination and cell growth. ALCAR supplementation after brain injury in rats did improve memory and long-term brain function. Additional studies are needed in humans.[46]

Fish Oils and Other Long-Chain Polyunsaturated Fatty Acids:

Omega-3 polyunsaturated fatty acids (n-3 PUFA), omega-6 polyunsaturated fatty acids (n-6 PUFA), and other long-chain dietary PUFAs such as docosahexaenoic acid, eicosapentanoic acid, and *arachidonic acid* (ARA) have demonstrated anti-inflammatory effects on the brain in preclinical studies. It is reasonable to postulate that they will have neuroprotective benefits in AD and may improve neurocognitive function. Additional studies are needed in humans.[47]

The Role of Herbs in Cognition

Ginseng:

Ginseng (order: Apiales; family: Araliaceae; genus: *Panax*) is one of the most popular traditional herbal medicines and has been used all over the world for more than 2000 years. It has been touted as having many beneficial effects on memory, attention, and thought processing and for promoting overall improvement in the wellbeing of a healthy individual. Ginseng has also been reported to

have anti-anxiety and antidepressant properties.[48] It may also have neuroprotective effects in AD, in that it reduces beta-amyloid formation, tau hyperphosphorylation, and oxidative stress. It also reduces the severity of major depression, stroke, Parkinson's disease, and multiple sclerosis.[48]

In a few studies, ginseng has been shown to be effective in reversing cognitive decline in patients with AD.[48-50] Unfortunately, most of these studies—which include a systematic review and meta-analysis of randomized controlled clinical trials—have provided inconclusive evidence about its effects in patients with AD. **The main limitations of available studies are the small sample sizes, poor methodological qualities, and lack of placebo controls.** Larger, well-designed studies are needed to test the effect of ginseng on AD.[50]

Ginseng and its byproducts, which include Ginsenoside Rb 1 and Ginesonoside Rg 1, are thought to improve learning and memory in hippocampus-dependent tasks by enhancing choline acetyltransferase activity and inhibiting AChE activity in central cholinergic pathways. Ginseng has also been shown to attenuate beta amyloid-1-42-induced neurotoxicity and tau hyperphosphorylation at multiple AD-related sites.[51]

The most commonly reported adverse effects of ginseng include insomnia, breast pain, palpitations, high or low blood pressure, headache, loss of appetite, diarrhea, itching, rash, dizziness, mood changes, and vaginal bleeding.[49]

Ginkgo Biloba:

Ginkgo biloba is another herbal medicine that has been marketed to adults who are cognitively intact with claims that it can enhance neuropsychological functioning. An early large-scale clinical trial of the efficacy of *ginkgo biloba extract* (GBE) showed enhancement of the neuropsychological/memory processes in cognitively intact adults aged 60 years and above.[52] Another study in healthy young volunteers in the United Kingdom suggested a dose-dependent effect on cognition after the short-term administration of ginkgo biloba, but there was a concern about its ability to enhance memories of negative experiences.[53]

There is mixed evidence supporting the efficacy of GBEs in MCI and dementia. Some subgroups of patients with AD or MCI may benefit. Overall, however, GBEs were found to be safe.[54]

A meta-analysis of randomized clinical trials regarding its effectiveness and safety in MCI and AD revealed that gingko biloba, in combination with conventional medicine, is superior for improving cognitive function compared with conventional medicine alone. The authors of this study advise caution when interpreting their findings, however, because the sample sizes were small, the findings were inconsistent, and methodological quality of some of the trials included in this analysis were poor to moderate.[55]

The mechanism of action for gingko biloba remains largely unknown. In animal studies,[59] it has been shown to enhance neural perfusion by inhibiting platelet-activating factor, increasing glucose consumption in hypoxic and ischemic environments,[56] and enhancing neurotransmission by increasing the number of cholinergic receptors in the hippocampus.[57,58] Gingko biloba is also thought to improve neurocognitive abilities by providing neuroprotection through its antioxidant properties[56,58] and by promoting neural plasticity in the hippocampal area.

High doses of gingko biloba can cause diarrhea, restlessness, nausea, and subarachnoid hemorrhage.[59]

Huperzine A:

Huperzine A, an active *Lycopodium* alkaloid extracted from a traditional Chinese herb (*Huperzia serrata* [Qian Ceng Ta]),[60] is a natural, potent, selective, and reversible *acetylcholinesterase* (AChE) inhibitor. Small early studies suggest that it can promote improvement in memory and protection of nerve cells, thereby slowing the rate of cognitive decline associated with AD. It is a licensed anti-AD drug in China, but it is only available as a nutraceutical in the United States.[60]

A systematic review and meta-analysis of randomized clinical trials showed that huperzine A may have beneficial effects on cognitive function, ADL, and global clinical assessment in individuals with AD.[61] Similar to studies of other herbal remedies, however, these study findings should be interpreted with caution because of the poor methodological quality of the some of the trials included in this analysis.

Long-term safety data are lacking for huperzine A, given that most studies of huperzine A were conducted

over 3 months or less.[61] Therefore, more studies are needed to determine the possible benefits and long-term risks of this agent.

The neuroprotective effects of huperzine A may be mediated through its ability to protect against amyloid beta-induced oxidative injury and mitochondrial dysfunction as well as its ability to inhibit AChE, upregulate nerve growth factor, and antagonize *N*-methyl-d-aspartate receptors. It has been proposed that the neuroprotective effects of huperzine A are mediated through the mitochondria.[60,] The recent discovery that huperzine A may reduce the accumulation of iron in the brain lends further support to the argument that it may slow the course of neuronal death considerably and, thus, serve as a potential disease-modifying agent for AD and other neurodegenerative disorders.[61, 62] Its side effects include nausea and vomiting.

The Alzheimer's Association recommends not using huperzine A with other prescribed cholinesterase inhibitors, such as *donepezil* (Aricept), *rivastigmine* (Exelon) or *galantamine* (Razadyne) because of a risk of serious side effects.

Yokukansan:

The traditional Japanese herbal Kampo medicine known as yokukansan was used as early as the Ming dynasty (1555 AD) to treat aggression and restlessness in children. A millennium before, it was part of the traditional Chinese medicine Yi-Gan-San.[63]

Yokukansan has been reported to reduce the severity of the behavioral and psychological symptoms of dementia—including excitement, aggression, and hallucinations—without causing severe adverse effects.[63]

In China, yokukansan contains several powdered herbs: 4 parts *Atractylodis lanceae* root, 4 parts *Poria*, 3 parts *Cnidium* root, 3 parts *Uncaria uncis* cum ramulus, 3 parts *Angelica* roots, 3 parts *Bupleurum* root, and 1.5 parts *Glycyrrhiza* root. It is prepared by blending these herbs and administering them at a dosage of 2.5 g three times daily. In addition to dementia, this formula has been used to treat developmental disorders in children (e.g., autism spectrum disorders, aggression, severe tantrums, impulsivity, and pervasive developmental disorders). Yokukansan has also been found to be helpful in treating neurolepsis-induced tardive dyskinesia, Huntington's disease, neurosis, and restless leg syndrome.[63]

Matsuda and colleagues[64] conducted a systematic review and meta-analysis of patient data from randomized controlled trials in which the *Neuropsychiatric Inventory* (NPI) was used to evaluate behavioral and psychological symptoms of dementia. Their results suggest that Yokukansan has a beneficial effect on NPI and ADL scores and that it is well tolerated.[63, 64]

In other clinical trials of yokusansan in AD patients, no evidence of any effect on behavioral and psychological symptoms of dementia was observed, but it was shown to cause some improvement in agitation, aggression, and hallucination without causing adverse events.[64-66]

In animal studies, yokusansan and its bioactive ingredients demonstrated neuroprotective,[67] anti-stress, and anti-inflammatory effects while promoting neuroplasticity.[68]

Sage:

Limited in vitro animal studies and preliminary human studies suggest that the genus *Salvia*, commonly known as sage, includes some species that improve cognitive activity, have strong antioxidant activity, and protect against neurodegenerative disease. Studies in humans have been limited to specific species with varied extracts, small sample sizes, and short treatment duration. The majority of research with AD patients involved a single administration.[6]

Table 1:
Overview of Vitamins & Supplements

Vitamins & Herbs	Potential Benefits	Risks
Vitamin A	• Reduces rate of cognitive decline • Helps regenerate degenerating neutrons • Protects healthy neurons from degeneration	• Excess might cause toxicity
Vitamin B	• Reduces rate of cognitive decline • Pyridoxine, folic acid, or cobalamin decreases homocysteine levels, which causes a decline in oxidative stress • Reduces rate of brain atrophy	• Cobalamin deficiency can cause neurological and cognitive decline • Pyridoxine, folic acid, or cobalamin deficiency causes hyperhomocysteinemia, which increases ROS and oxidative stress • Folate deficiency causes an accumulation of tau tangles and beta amyloid protein leading to cerebral atrophy
Vitamin C	• Increases level of superoxide dismutase, which decreases oxidative stress • Alters oligomerization of beta amyloid protein, which decreases the progression and development of AD	
Vitamin D	• Enhances nerve function and detoxifies nerves • Vital for brain development	
Vitamin E	• Increases rate of superoxide dismutase regeneration • Reduces oxidative stress • Reduces rate of progression/development of AD	• Deficiency leads to early destruction of neurons and inability of neurons to be repaired
Trace Minerals		
Iron	• Essential for perinatal brain and neurocognitive function	• Deficiency leads to poor brain development and function • Excess may increase oxidation and risk of dementia
Zinc		• Deficiency in pregnancy leads to poor neurocognitive development of fetus
Magnesium	• Improves synapse function in animal models	
Nutritional Supplements		
ALCAR	• Improves energy • Decreases oxidative stress • Prevents cell death	
Fish oil & LC Fatty Acids	• Anti-inflammatory effect on brain cells	
Ginseng	• Improves hippocampus-related memory and learning	• Adverse effects include insomnia, breast tenderness, palpitation, hyper/hypotension, headache, loss of appetite, vaginal bleeding, itching, rash, mood changes
Ginkgo biloba	• Dose-dependent improvement in cognition • Decreases oxidative stress	• Enhances memory of negative experiences • Diarrhea, restlessness, nausea, subarachnoid hemorrhage
Huperzine A	• Improves memory and protection of nerve cells • Protects against oxidative injury and mitochondrial dysfunction	• Nausea and vomiting • Increased risk of serious side effects if used with other cholinesterase inhibitors
Yokukansan	• Improves behavior and physiologic symptoms of dementia • Improves agitation, aggression and hallucination • Neuroprotectant • Anti-stress and anti-inflammatory properties • Improvement in neuroplasticity	
Sage	• Strong antioxidant activity • Protects against neurodegenerative diseases • Cognition-enhancing effect	

Conclusion

Data estimates reveal that 35.6 million people were living with dementia in 2010 and suggest that this number will almost double every two decades, reaching 65.7 million in 2030.[2] As treatments and interventions continue to be investigated, the market for vitamin and herbal supplements continues to grow. Some studies suggest that B vitamins and vitamin D have a protective effect on cognition, but the exact effects of vitamin and herb supplementation remain unknown. Studies to date have been insufficient, inconsistent, or lacking power.[70] It is particularly difficult to draw conclusions from herbal medicine studies because of differences in the quality, potency, and purity of the extracts used in these studies. Additionally, safety data for herbal supplements at higher doses are lacking. At present, there is insufficient evidence to recommend any specific over-the-counter supplement to reduce the risk of cognitive decline in patients with normal cognition or MCI. Randomized, controlled studies in humans with larger populations at multiple centers are needed to determine the true benefit of each item and provide a better understanding of relationships between vitamins/herbs and cognition.

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Multiple-Choice Questions

37. Which of the following is *not* one of the neurocognitive domains that form the basis of neurocognitive disorder diagnoses?

A. Executive function

B. Arithmetic

C. Learning and memory

D. Language

38. Homocysteine, a known cause of neuronal toxicity, is metabolized by which of the following vitamins?

A. Vitamin A

B. B vitamins (pyridoxine, folic acid, and cobalamin)

C. Vitamin C

D. Vitamin D

39. Which vitamin is involved in the regeneration of damaged neurons, as well as maintaining the general health of a neuron?

A. Vitamin A

B. Vitamin B complex

C. Vitamin C

D. Vitamin D

40. Ginseng has been demonstrated to be effective in improving cognitive decline, but the evidence is considered inconclusive for all of the following reasons *except*:

A. Small sample sizes

B. No placebo control

C. Poor methodology

D. Side effects

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Best Practices in CME

Vitamins, Minerals, and Herbs: Their Effects on Neurocognitive Disorders

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This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Alzheimer's disease (AD) remains the sixth leading cause of death in the United States; data estimates suggest that the diagnosis of dementia will almost double every two decades. With increased interest in supplements to promote health, it is important for clinicians to be aware of the evidence for the safety profile and potential benefits of vitamins, minerals, and herbs for cognition. This lesson will review common vitamins, minerals, and herbs used to preserve cognition and/or slow cognitive decline.

Key Point 1: Neurocognitive disorders (NCDs)

The DSM-5 diagnostic category of neurocognitive disorders includes delirium as well as syndromes of major and mild NCDs. The criteria for an NCD are based on six cognitive domains: (1) complex attention, (2) executive function, (3) learning and memory, (4) language, (5) perceptual-motor, and (6) social cognition. For a diagnosis, the primary clinical deficit must be cognitive function and it must be acquired rather than developmental.

Key Point 2: Alzheimer's disease

AD is the most common cause of dementia and the sixth leading cause of death in the United States. An increase in oxidative stress, coupled with a decrease in cellular defense mechanisms, contributes to the pathogenesis of AD. Because some vitamins are potent antioxidants and have been shown to decrease oxidative stress and neuronal damage, supplements are being investigated as potential treatments for AD and other neurocognitive disorders.

Key Point 3: Dementia Prevalence and Treatment

Data estimates suggest that the number of individuals living with dementia will double every two decades and reach 65 million by the year 2030. As the population ages, there will be increased interest in not only medical treatments for neurocognitive disorders, but also alternative options through nutritional supplementation.

Key Point 4: Vitamins and Herbs

An increasing number of supplements are being used to improve the health status of older adults and curb acquired cognitive decline. It is important for clinicians to be aware of the potential benefits, as well risks, of prescribing common vitamins, minerals, and herbs for patients to address cognitive function. At present, there is insufficient evidence to recommend any specific over-the-counter supplement to reduce the risk of cognitive decline.

Notes

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Qualitative Investigation of Effects of 9/11 Attacks on Individuals Working in or Near the World Trade Center

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KEY WORDS: Disaster • Terrorism • Qualitative research • Posttraumatic Stress Disorder

LEARNING OBJECTIVES: On completing this lesson, clinicians will be able to (1) describe the current research of the psychosocial effects of the attack on the *World Trade Center* (WTC) in New York City on September 11, 2001 (9/11); (2) describe how this disaster was experienced by employees of companies located in or near the WTC during the attack; and (3) distinguish the experiences of workers at "Ground Zero" (i.e., in the WTC) from those working beyond Ground Zero during the attack.

LESSON ABSTRACT: The aftermath of the 9/11 attack on the WTC introduced challenges beyond those associated with survival and the emotions that developed immediately thereafter. Thus far, most of the research into these effects has focused on *posttraumatic stress disorder* (PTSD); consequently, many other disaster-related psychosocial issues may have been overlooked. A qualitative study of the experiences of individuals working in New York City at the time of the attack was conducted based on the findings from 21 focus groups involving 140 participants.[1] The focus group participants were recruited from companies located in the WTC and companies nearby that were affected by the attack. An analysis of interactions within these focus groups revealed five major themes: (1) disaster experience; (2) emotional responses (which included two subthemes: posttraumatic stress symptoms and other emotional responses); (3) workplace issues; (4) coping strategies; and (5) issues of public concern. The study findings demonstrate that the effects of the 9/11 WTC terrorist attack were far more complex and nuanced than the circumscribed disaster trauma-related psychopathology that has emerged as a major focus of disaster-related mental health literature.

COMPETENCY AREAS: This lesson addresses a gap in our knowledge of the psychosocial issues that can arise as a result of a terrorist attack. The consistent focus in the literature on PTSD and posttraumatic stress symptoms may cause clinicians and policymakers to focus their response too narrowly on the treatment of this diagnosis. Upon completing this lesson, readers will have a better understanding of the complex nature of such experiences and how open-ended and systematic assessments can be combined to gain a more in-depth understanding of the psychosocial effects of such disasters.

Introduction

The frequency with which disasters occur around the world is on the rise, affecting more than 150 million people annually.[2] Disasters are generally classified as one of three types: (1) natural disasters; (2) technological accidents; and (3) intentionally caused disasters, including terrorism. The purpose of this review is to explore the findings of a qualitative study of survivors of the single largest terrorist attack to occur on American soil in the context of this attack and in the context of actions of terrorism more broadly. On September 11, 2001, terrorists flew airplanes on domestic flights into targeted buildings in the United States, including the *World Trade Center* (WTC) towers in New York City. Approximately 3000 people were killed;[3] an additional 15% of New York City residents were affected through direct exposure to trauma during the attack, rescue efforts, loss of employment or property, or the death of a family member or friend.[4] Over weeks and months following the attack, some survivors developed various forms of disaster-related psychopathology, especially *posttraumatic stress disorder* (PTSD)[5] and major depressive disorder.[6]

Media coverage of this attack, now known as the 9/11 attack, was extensive and far-reaching. News stations and network outlets pre-empted regular programming to broadcast attack-related events live. Millions of Americans watched intently, fixated on the horrific images of airplanes crashing into the WTC towers and the towers burning then crumbling. Continued media coverage, including repeated replay of the towers collapsing and graphic images of individuals falling from the burning towers, elicited strong emotional responses from viewers.[7]

In the aftermath of these attacks, new challenges beyond those of survival and coping with the immediate experience of strong emotions were introduced. The tasks ahead included restoration of productivity and rebuilding workplaces that were destroyed or severely damaged, coping with loss,[8] and managing fear and new beliefs about the nature of the security and safety of the United States.[9] Because the perpetrators of these attacks were from the Middle East, domestic relations with Muslims in the United States deteriorated,[6] resulting in a 78% increase in anti-Muslim hate crimes.[10]

President George W. Bush initiated legislation addressing domestic and international responses to terrorism that were designed to ensure public safety, including stiffer enforcement of new domestic and international travel restrictions ("President Bush signs Homeland Security Act," 2002). He also initiated the "War on Terror," which included Operation Enduring Freedom in 2001 and Operation Iraqi Freedom in 2003. The broad societal effects of the 9/11 attacks have been deep and long-lasting, altering the character of American life and politics.

Current Knowledge about the Psychosocial Effects of the 9/11 Attacks

Most of the research on the psychosocial sequelae of the 9/11 attacks has consisted of quantitative studies. Much of it was launched almost immediately after the attacks, some as soon as 3 to 5 days thereafter,[11] others within several weeks.[12, 13] Data were collected rapidly using random-digit dialing and brief self-report symptoms surveys. **Research on the effects of the attacks on mental health has consisted largely of quantitative estimates of psychiatric symptoms and disorders, especially posttraumatic stress symptoms and PTSD.**[14, 15, 16] The most common psychiatric disorder associated with terrorism and other types of disasters has been PTSD.[2, 14, 17, 18, 19]

Chen (2006) examined trends in quantitative research of the effects of terrorism on mental health,[20] which has traditionally been based on survivors of direct exposure to trauma. The 9/11 attacks served as a seminal point in this research, however, in that it allowed investigators to broaden their subject base to include individuals who had not been directly exposed to trauma. The issue of trauma exposure is highly relevant for a diagnosis of PTSD following a terrorist attack, given that a diagnosis of posttraumatic stress symptoms and PTSD requires exposure to an event that can be defined as traumatic, according to accepted diagnostic criteria for PTSD.[21] Symptoms identified in individuals who were not exposed to trauma cannot be considered representative of posttraumatic stress, although they may be considered indicators of disaster-related distress beyond PTSD constructs.[16] When such symptoms are considered as contributing to PTSD, the result can be a gross overestimation of PTSD, especially in populations that include many individuals who had not been exposed to trauma.[16] This is an important

consideration for research into incidents of a massive scope in which a large population may have been affected, although not necessarily through direct exposure to the traumatic aspects of the event.

Research that focuses on PTSD and posttraumatic stress symptoms may miss other disaster-related issues.[22, 23, 24] In the case of the 9/11 WTC attack, these included medical sequelae—such as respiratory diseases (e.g., bronchitis and asthma) and gastrointestinal reflux—and an overall increase in healthcare utilization among the 71,000 individuals enrolled in the WTC Health Registry who had physical proximity to the 9/11 attack.[25-32]

Application of Qualitative Methods to Identify Gaps in Disaster-Related Mental Health Research:

A limitation to the use of quantitative methods to investigate the effects of a disaster on mental health is that they are essentially reductionist in nature, limiting researchers to topics that have been defined based on selected well-defined constructs. Their use is limited by the very complex nature of disasters themselves, which present many unknowns. The consequences of such events vary from one disaster to another, across various settings and timeframes and across individuals and groups.[16] Qualitative research methods are useful alternatives for investigating events with many unknowns or events that are too complex for straightforward quantitative measurement, such as a disaster. The nondirect approach to inquiry that is inherent in qualitative research may allow a broader examination of the psychosocial consequences of disasters, thereby providing the potential for refeshing insights that are not realized in more focused quantitative studies.

Phenomenological approaches to qualitative research can help investigators understand common factors among individual experiences by describing common themes and interpretations. This can be accomplished using individual interviews, focus groups, and grounded theory approaches. Individual interviews can be used to collect personal perspectives that capture one person's experience uniquely. Focus groups permit investigations of greater complexity by encouraging group members to interact by discussing their experiences and developing an aggregate understanding of experiences that is not possible through individual interviews. Grounded theory allows investigators to develop an integrated understanding by saturating qualitative data to develop theories about a specific topic under investigation. Each of these methods brings a unique approach to qualitative data collection and yields useful types of information.

The focus group is one of the most popular qualitative methods of investigation. It was deveoped at Columbia University in 1940 and has been used over the past 40 years in the private sector by marketing resarchers.[33, 34] In the 1980s, it was adopted by social scientists and the field of sociology as a formal method of research.[35, 36] Focus groups can be used in a qualitative, systematic, and strategically planned manner to obtain and examine the content of the discussions, dialogues, and behaviors of representative groups of interest, capitalizing on the material that emerges from group interactions and discussions.[37,38] Each focus group is led by a faciliator who moderates the discussion around a specific topic and helps participants feel comfortable in open conversations.[34] Under the guidance of the facilitator, the group is largely unstructured; this supports the emergence of unplanned dialogue, narration, individual ideas, interactive discussions, and an in-depth explication of diverse viewpoints.[39, 40]

Qualitative Research on the 9/11 Attack on the WTC:

A search of the literature for qualitative studies of the 9/11 attacks on the WTC and the Pentagon using the specific search terms "qualitative," "focus groups," and "narrative" yielded 14 published articles, more than half of which were written by a single research team led by North and Pollio. **The qualitative method used most often involved focus groups (n=11)[1, 31, 41, 42, 43, 44, 45, 46, 47, 48] followed by individual qualitative interviews (n=3)[32, 49, 50] and written narratives (n=1).[51]** The populations studied in this research included people who were in the WTC during the attack and others affected by the disaster (e.g., rescue workers and flight attendants), children, adult, and senior populations. Identifiable analyses were primarily thematic in focus (n=11); three used a narrative approach. **Rather than focus on PTSD or psychopathology directly, the qualitative literature examined disaster-related experiences, incorporating trauma exposure and response only as it emerged naturalistically during discussions by the study participants.**

Focus Group-Based Study of the Effect of Trauma Exposure on 9/11:

In 2015, North and colleagues[1] carried out a qualitative study of "the thoughts, feelings, perceptions and concerns about the 9/11 terrorist attacks" of 140 individuals who were in New York City during the attack. The study participants, who were recruited from companies located in the WTC site during the time of the attack ("Ground Zero" groups N=60) or from companies located nearby ("Non-Ground Zero" N=80),[1] were divided into 21 nondirect focus groups that met approximately 2 years after 9/11. The Ground Zero focus group consisted of nine groups of employees (3 from a company in the North Tower, 4 from a company in the South Tower, and 2 from a social service agency located across the street from the WTC); the non-Ground Zero focus groups consisted of 12 employee groups (2 from a social service agency located 1.5 blocks away from Ground Zero; 5 from a company located 2 miles from Ground Zero; and 5 from an affected airline, with separate groups for flight attendants, aircraft mechanics, and managers). The focus group facilitators were directed to provide only minimal guidance to avoid influencing discussions among group members with any preconceptions of the researchers. Investigators found that the only participants who had been subjected to direct trauma exposure during the attacks (i.e., there was a threat to life or limb, as defined in the criteria for PTSD in the *Diagnostic and Statistical Manual for Mental Disorders, 4th Edition Text Revised* [*DSM-IV-TR*]) were from companies at Ground Zero.[52]

An analysis of the discussions in all of the focus groups revealed five major themes: (1) *Disaster Experience*; (2) *Emotional Responses* (with 2 subthemes: Posttraumatic Stress Symptoms and Other Emotional Responses); (3) *Workplace Issues*; (4) *Coping Strategies*; and (5) *Issues of Public Concern*.

The *Disaster Experience* theme pertained to immediate experiences of the attack, ie, learning about the attack through immediate exposure either at the site or by observing them at a safe distance or through media accounts. This theme was found in 15% of all coded passages (18% of passages from the Ground Zero groups and 11% of passages from the non-Ground Zero groups). **Additionally, Ground Zero participants discussed personal encounters extensively, whereas those in the non-Ground Zero groups primarily expressed concern about the difficulties of others.** In both groups, participants expressed horror and disbelief in response to the attack; however, only the Ground Zero participants described personally experiencing initial shock from direct exposure or by eyewitnessing danger, reporting the physical jolt when the planes hit the tower, witnessing individuals falling from the towers, rushing to get to safety in the midst of the extensive surrounding destruction, and fleeing to escape the cloud of dust and debris from the collapsing buildings. By contrast, the non-Ground Zero participants generally received information about the attacks from others and from the news media.

The *Emotional Response* theme had the highest absolute number of coded responses (34% of all coded passages: 35% for Ground Zero groups; 33% for non-Ground Zero groups). Passages coded for this theme described heightened emotional arousal, repeated frightening mental images of the witnessed trauma, hypervigilence, a general sense of dread, and sorrow over losses. This theme included two subthemes: posttraumatic stress symptoms and other emotional responses. In the Ground Zero groups, more than half (58%) of these passages were coded for Other Emotional Responses and 42% for posttraumatic stress symptoms. By contrast, a clear majority (83%) of Emotional Response passages from the non-Ground Zero groups were coded for Other Emotional Responses versus 27% for Posttraumatic Stress Symptoms. All of the participants shared prominent re-experiences of images of the attacks. The Ground Zero participants were haunted by close-up, in-person images based on their own experience of the attacks, whereas the non-Ground Zero participants reported intrusive reexperiences primarily of media images. The Ground Zero participants also described grief over the loss of coworkers and friends, as well as their own material possessions. By contrast, the non-Ground Zero participants primarily expressed concern for the emotional wellbeing of their own families (especially their children), friends, and neighbors.

The *Workplace Issues* theme (9% of all coded passages: 12% for Ground Zero groups; 6% for non-Ground Zero groups) consisted of descriptions of post-9/11workplace adjustments and the concern of both employees and managers about the effects of the attacks on their careers and finances. It also included a discussion of post-9/11

workplace recovery services. The main workplace concerns in the Ground Zero groups pertained to readjustment to the post-9/11 work environment and difficulties acclimating to unfamiliar new work environments. Their discussions reflected crowded workplace conditions and a lack of resources, yet they indicated that coming together with their colleagues when they returned to work was comforting and greatly facilitated their progress toward emotional recovery. Individuals in managerial positions reported feeling responsible for helping their employees with the readjustment process, particularly by making accommodations for the temporarily reduced functional and productive capacity of the workers during the very emotional early postdisaster period. The major workplace concerns of the non-Ground Zero participants involved broader societal economic and financial issues.

The *Coping Strategies* theme (13% of all coded passages: 12% for Ground Zero groups; 13% for non-Ground Zero groups) consisted of a discussion of activities or intiatives designed to help the participants process their feelings about their 9/11-related experiences. Coping was achieved through emotional and social support provided by family and friends, professional mental health assistance, and spiritual and religious resources. Distinct differences in coping strategies were identified for Ground Zero versus non-Ground Zero participants. The Ground Zero participants described their workplace as a major means of helping them cope with their feelings. They talked about throwing themselves back into their work and receiving unparalleled emotional support from their coworkers. Some stated that they did not feel that people who had not personally experienced the attack could understand their experience as well as their coworkers, who experienced the attack with them. They also said that they made efforts to protect their family members from disturbing details about their experiences. By contrast, the non-Ground Zero participants said they obtained most of their emotional support from family members, through therapy, or through their own personal spirituality or religious community resources.

The *Issues of Public Concern* theme (29% of all coded passages: 23% of Ground Zero groups; 36% of non-Ground Zero groups) included discussions of political, cultural, and media aspects of the 9/11 attack. Concern was expressed regarding the absence of national foresight for the attacks, insufficient emergency responses to the attacks, issues of personal safety, and the media's portrayal of the attack. The Ground Zero groups focused on the perceived lack of preparedness and concern for their own personal safety during the attack. They were specifically troubled by the lack of organization in the emergency response, disruption of communication systems by the attack, and perceived inefficient and unfair distribution of resources. They also criticized the media's intense and seemingly endless repetition of images of the disaster, especially the graphic images of individuals falling from the burning towers to their deaths. By contrast, discussions in the non-Ground Zero groups focused on the potential for future terrorist attacks and the economic consequences of the 9/11 attacks, including their own personal financial struggles and the nation's economic future.

Discussion

The extant literature on the effects of the 9/11 terrorist attacks on mental health has largely consisted of quantitative studies of posttraumatic stress symptoms and PTSD.[14, 15, 16] A qualitative approach using focus groups (North et al. 2015)[1] provided a broader examination of the experiences and perceptions of the attack on New York City. These findings demonstrated that the effect of that experience was far more complex and nuanced than the circumscribed measurement of psychopathology associated with disaster-related trauma. Importantly, findings from this study revealed that posttraumatic stress responses represented only a minority of the topics of discussion in the focus groups, even among individuals who worked for Ground Zero companies.[6]

Many similarities and differences emerged between the Ground Zero and non-Ground Zero focus groups as participants freely described their experiences and concerns in nondirected discussions. A common feature across all groups was emotional distress and anguish. Emotional responses other than those reflecting posttraumatic stress symptoms were predominant, most markedly in the non-Ground Zero groups. In addition to the greater amount of discussion of posttraumatic stress responses in the Ground Zero groups compared with the non-Ground Zero groups, major differences in the content of these discussions pertained to the focus on people (self vs others) and time (present vs future). The Ground

Zero groups focused on their own personal experiences in the period immediately following the disaster, whereas the non-Ground Zero groups focused on the experiences of others and included the broader community, the welfare of the country, and the possibility of terrorist attacks on the United States in the future.

After the 9/11 attacks, there was a surge in public support for the expansion of surveillance, implementation of national identification cards, passage of stricter immigration laws, and increased international military pressure.[53] In response, President George W. Bush signed into law two important pieces of legislation: (1) the USA Patriot Act (Uniting and Strengthening of America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism), signed into law on October 26, 2001, primarily "to deter and punish terrorist acts in the United States and around the world [and] to enhance law enforcement investigatory tools";[54] and (2) the Homeland Security Act, signed into law on November 25, 2002, to prevent terrorist attacks in the United States, reduce US vulnerability to terrorism, minimize damage from any future terrorist attacks, and assist in recovery from terrorism (Homeland Security Act, 2004).[55] The USA Patriot Act was designed to improve national counterterrorism abilities by allowing the use of wiretapping and other forms of surveillance that have been used to investigate organized crime and drug trafficking. Importantly, it also permitted emergency disclosure of electronic communications and a reduction in the number of restrictions required for law enforcement to search telephone, social media, and other forms of electronic communication, as well as health records, in the interest of protecting US lives from domestic terrorism.[54] The Homeland Security Act created a new cabinet position with the authority to investigate potential terrorist threats and obtain any information it needs to prevent future attacks.

After the 9/11 attacks, Americans grew increasingly suspicious and hostile toward certain minority groups;[56, 57] this resulted in major shifts in societal behaviors reflecting racial/ethnic prejudice (North, et al., 2015a).[1] Hate crimes against Arabs, Muslims, and people perceived to be members of these groups increased 17-fold[58, 59, 60] shortly after the 9/11 attacks and continued to increase thereafter.[61, 62] Consequently, members of many minority groups experienced an increase in fear and anxiety[53] that was further reinforced by changes in policies that emerged in the aftermath of the 9/11 attacks. These changes resulted in the detention of more than 1200 people of middle eastern descent.[56]

Future Directions in Disaster Research

An important finding of the qualitative study of 9/11 by North et al. (2015a)[1] was that nondirected focus group discussions were less likely to be about posttraumatic stress reactions and PTSD than about emotional responses and concerns. This suggests the possibility of bias in existing quantitative research due to its narrow focus on posttraumatic stress responses. This unexpected finding has implications for future approaches to this type of research. It suggests the need to proceed in a circumspect manner to ensure that all important constructs are examined. A sequential approach could begin with qualitative perspectives of those affected by the event (victims, providers, and policymakers), as was done by North and colleagues (2015a).[1] Once the concerns of diverse stakeholder populations have been identified, quantitative methods can be used to evaluate the results (possibly modified by the results of qualitative studies) to yield a comprehensive, systematic, rigorous, and robust approach to the effects of terrorism on mental health. This combination of qualitative and quantitative methods of inquiry may reveal unique insights that can be validated further through quantitative investigation informed by earlier qualitative and quantitative findings.

More qualitative research with even broader populations (e.g., including rescue and recovery workers; mental health professionals; families of the deceased) could facilitate the ability of researchers to identify other important mental health responses to terrorism. The application of still other qualitative methods, such as grounded theory, might further enrich the findings of one-pass qualitative studies, such as the focus group study by North and colleagues (2015a).[1] Finally, a focused examination of public responses to media coverage and public policy could help guide future efforts to respond to terrorist incidents more effectively.

Conclusion

We have attempted to clarify the means of combining qualitative and quantitative research methods to expand our current knowledge of the effects of terrorism and other types of disasters. Quantitative research has provided information about posttraumatic stress symptoms and PTSD, thereby identifying the need for mental health interventions. A more limited body of disaster-related qualitative research, exemplified by the focus group study by North and colleagues,[1] may help us identify gaps in our knowledge of these matters and find new directions for disaster mental health interventions and research.[1]

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L003414

Multiple-Choice Questions

41. Most of the published research on 9/11 is:

A. Qualitative in approach.

B. Focused on PTSD.

C. Collected more than three years after the event.

D. Used written surveys.

42. The limited qualitative research on 9/11 primarily:

A. Used a grounded theory approach.

B. Focused on PTSD.

C. Used focus groups and unstructured interviews.

D. Used individual interviews with semi-structured instruments.

43. The qualitative study of 9/11 conducted by North and colleagues (North, Barney & Pollio, 2015a):

A. Included a sample comprising individuals all of whom had been directly exposed to trauma.

B. Completed a brief screene for PTSD.

C. Used a systematic protocol to explore specific aspects of 9/11.

D. Used a non-directive approach to allow issues emerge naturalistically.

44. In the North and colleagues study (North, Barney & Pollio, 2015a), comparisons between data collected from Ground Zero groups versus data collected from non-Ground Zero groups at companies nearby revealed:

A. The Ground Zero groups focused more initially on their own experiences, the groups conducted at companies nearby focused on experiences of others.

B. No differences between the two groups.

C. A greater focus on issues of PTSD symptoms in the groups conducted at companies nearby than in Ground Zero groups.

D. A greater focus on emotional distress and anguish in the Ground Zero group.

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Best Practices in CME

Qualitative Investigation of Effects of 9/11 Attacks on Individuals Working in or Near the World Trade Center

By Edward Randle, PhD, MSW; E. Whitney Pollio, EdD, MSN;
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ID#: L003414

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The aftermath of the 9/11 attack on the WTC introduced challenges beyond those associated with survival and the emotions that developed immediately thereafter. Using research conducted by the authors, this lesson aims to demonstrate that the effects of the 9/11 WTC terrorist attack were far more complex and nuanced than the circumscribed disaster trauma-related psychopathology that has emerged as a major focus of disaster-related mental health literature.

Key Point 1: Background

Although disaster-related psychopathology is disproportionately prevalent among those directly exposed to 9/11 trauma, the experience of individuals directly and those nearby reflect much broader concerns and more complex responses.

Key Point 2: Need for Multidisciplinary Approaches

To understand the effect of events like the 9/11 terrorist attack, researchers need to move beyond a sole focus on quantitative, deductive methods focusing primarily on psychopathology. Qualitative, inductive methods provide complementary information and allows the possibility for uncovering findings unavailable to reductionistic approaches.

Key Point 3: Response Variances of Ground Zero vs non-Ground Zero Groups

Many similarities and differences emerged between experiences reported by individuals at Ground Zero and those nearby. A common feature across all groups was emotional distress and anguish. In addition to the greater amount of discussion of posttraumatic stress responses in the Ground Zero groups compared with the non-Ground Zero groups, major differences in the content of these discussions pertained to the focus on people (self vs others) and time (present vs future).

Notes

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Assessing PTSD in Ethnic and Racial Minorities: Trauma and Racial Trauma

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Destiny M. B. Printz; Chad T. Wetterneck, PhD

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

KEY WORDS: Posttraumatic stress disorder • Ethnic differences • Symptom assessment • Psychotherapy • Racism

LEARNING OBJECTIVES: On completing this lesson, the clinician will be able to (1) recognize various factors that contribute to an increased risk for *posttraumatic stress disorder* (PTSD) in people of color; (2) identify underrecognized race-based traumatic experiences; and (3) indicate appropriate applications of assessment tools and treatments for race-based trauma and PTSD in people of color.

LESSON ABSTRACT: Ethnic and racially motivated traumatic events can cause PTSD in people of color. Unfortunately, this type of trauma is often not identified during clinical assessments. PTSD can persist without appropriate treatment, and failure to detect it may only prolong the distress further and increase the risk of developing and maintaining PTSD. This lesson presents up-to-date methods of detecting racial trauma, validated self-report and clinician-administered PTSD assessment tools that are appropriate to use with persons of color, and guidelines for selecting the most appropriate treatment for patients with race trauma-related PTSD. Additionally, common causes of racial trauma are identified and case examples are provided to help clinicians conceptualize racial trauma and support their ability to detect racial trauma-related PTSD in patients of color.

COMPETENCY AREAS: This lesson supports *patient care* and clinician *performance in practice* by providing current information and appropriate tools to identify and assess racial trauma-induced PTSD accurately in patients of color. It also summarizes treatments considered appropriate based on current research and *evidence-based practices* and identifies feasible methods of evaluation and support.

Introduction

Posttraumatic stress disorder **(PTSD) is a debilitating condition that is characterized in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) by five main criteria:[1] (1) exposure to a perceived life-threatening event or sexual violence; (2) re-experiencing the trauma (typically as intrusive memories and/or nightmares); (3) avoidance of trauma reminders (attempts to escape from or avoid external stimuli that appear to match components of the trauma, including thoughts or feelings associated with the trauma); (4) changes in mood and cognition (e.g., a more depressed outlook, a sense of a shortened future or of the world being inherently dangerous, losing trust in oneself/others, and self-blame for the trauma); and (5) trauma-related arousal and reactivity (e.g., hypervigilance [feeling "on edge"], increased irritability, an exaggerated startle response, and difficulty sleeping).**

PTSD has been linked to employment problems[2, 3] impaired relationships,[4, 5, 6] and a worsened quality of life.[7, 8] Comorbidity is the norm (~90%).[9, 10] Adults and adolescents with PTSD are at increased risk for suicidal ideation and attempts,[11, 12, 13] with the risk being greater for those who experienced maltreatment during childhood or violence and for those with a comorbid major depressive disorder.[10, 14, 15] PTSD is also associated with physical health problems,[10] including metabolic disease, joint disease, cardiovascular issues, chronic pain, lung disorders, and asthma.[16, 17]

Generally, PTSD does not go away on its own.[18, 19, 20] As a result, the duration of the somatic conditions accompanying it may be prolonged. Even when the comorbid physical ailments are accounted for, patients with PTSD tend to use greater amounts of medical services, including inpatient treatment.[21, 22] Thus, an accurate assessment and prompt institution of appropriate care is essential to reduce patient suffering and healthcare costs.

The accuracy of an assessment depends on the ability of the clinician to understand what constitutes a traumatic event in each population. Given that PTSD is seen worldwide (~4%; possibly higher in areas involved in war, facing natural disasters, etc.),[23, 24] with increased rates seen in the United States and Canada (6%-9% and ~9.2% respectively)[10, 25, 26]—in part possibly because of the diversity of the population in each country—the task of identifying risk factors for PTSD in each patient can seem quite daunting.[27, 28] In North and Central America, indigenous groups may be at increased risk for PTSD, but not for generalized anxiety or panic disorder; this also suggests a role for race, ethnicity, or sociocultural issues in the risk for PTSD.[29] Black and *Latinx* (gender-neutral term for Latino) populations in the United States appear to be at greater risk for PTSD than whites, whereas Asian individuals appear to be less likely to develop this disorder.[30, 31, 32] Estimates of trauma exposure among racial and ethnic groups are mixed, although people of color appear to be at greater risk for trauma related to maltreatment during childhood,[17, 33] immigration issues, war, or by witnessing domestic violence.[32] The expression of symptoms may also vary by race or ethnicity. For example, African-Americans with PTSD may demonstrate a more negative world view less heightened arousal than others, whereas Latinx patients may demonstrate physical symptoms and avoidance more often than members of other ethnic groups.[31, 34]

Complicating the process of making an accurate assessment is the disparity in access to services and quality of treatment across diverse populations. Studies have shown, for example, that black patients are less likely to receive treatment referrals or to be diagnosed with PTSD by a licensed psychiatrist or psychologist disability claims examiner; this, in turn, reduces their access to care.[35, 36] Furthermore, a black American with PTSD living in the inner city may never receive any mental health treatment.[37] In this lesson, we will shed light on important areas to consider in the assessment of PTSD in various populations.

Defining PTSD and Racial Trauma

The current diagnostic criteria for PTSD that appear in the *DSM-5* cross cognitive, behavioral, and affective presentations of the disorder.[1] Additionally, the *DSM-5* contains an important prerequisite for the identification and diagnosis of PTSD (referred to herein as "Criterion A"): a history of *trauma exposure*.

The *DSM-5* defines a traumatic event as one resulting from *direct exposure* to physical or sexual violence (e.g., a serious and fatal accident, combat experience, torture,

child abuse, or physical/sexual assault), *indirect exposure,* (i.e., learning about a traumatic event affecting a close family member or friend), or *repeated exposure* to traumatic events in an occupational setting.[1] **Certain experiences that are not covered under the "Criterion A" umbrella can still cause a traumatic reaction.** This has led to arguments for the legitimization of exposure to racist acts and other forms of oppression as traumatic events worthy of consideration in the diagnosis of PTSD.[38, 39] Carter explains that exposure to racial acts can trigger a traumatic reaction.[40] ***Racial trauma*** **can be defined as a traumatic response to race-related experiences that are collectively characterized as *racism,* including acts of prejudice, discrimination, or violence against a subordinate racial group based on attitudes of superiority held by the dominant group. Racial trauma can be caused by overt or covert actions carried out by individuals or society (e.g., aversive racism, modern/symbolic racism, racial microaggressions, etc.).** There is already strong evidence that over time, racial trauma can result in significant psychological and physiological damage in people of color, thereby contributing to various forms of psychopathology, including PTSD.[41, 42, 43]

Common Causes of Racial Trauma

Table 1 summarizes several forms of racial trauma that are commonly experienced by various ethnoracial groups.

Table 1:
Examples of Race-based Traumas That May Meet DSM-5 Criteria for PTSD

Common Racial Trauma	Examples of Criterion A Required for a Diagnosis of PTSD
Overt racial slurs and threats made in any environment by anyone	Perpetrator uses a negative racial/ethnic epithet to refer to the victim and/or threatens the victim with assault or death.
Police harassment, body searches, and assaults	Law enforcement officers assault the victim physically, issue threats, or search the victim's body for evidence of a crime (e.g., weapons, drugs).
Workplace discrimination	Coworkers express racially motivated threats or carry out physical assaults against the targeted individual in the workplace.
Community violence	Victim witnessed violence or was afraid for his/her life/personal safety or that of family members.
Distressing medical experiences	Victim has persistent fear for life of self/loved ones due to medical mistreatment.
Incarceration	Victim was physically or sexually assaulted while in prison.
Immigration difficulties	Victim experienced physical/sexual assault or robbery or feared for life of self/loved ones during the immigration process.
Deportation	Children witness violent confrontation and abduction of parents by law enforcement.

Overt Racial Slurs and Threats:

Implying that someone does not belong in a certain place and needs to leave "or else," referring to that individual using an ethnic or racial slur, or a combination of these two actions can be interpreted as a threat to commit bodily harm when the target is a person of color. Some of the examples described in Table 1 fit the criteria for trauma quite well, whereas others are associated with cultural learning that associates degrading language with violence. It is important to note that some clinicians may recognize such actions as evidence of overt racism and carry out their due diligence to denounce them, yet fail to provide investigative follow-up, even when the action in question qualifies as a Criterion A.

Police Harassment, Search, and Assault:

The ongoing epidemic of police brutality across the United States and the commission of extrajudicial killings of people of color that are considered "justified" on the basis of persistent racial stereotypes have had a negative effect on the social, emotional, and psychological development and well-being of all African-Americans, but particularly young African-American men.[44] Gallup poll data on attitudes and perceptions of the police from 2011 to 2014 show that 59% of white people have "quite a lot of confidence" in the police compared with only 37% of black people.[45] Men of color often report physical, psychological, and sexual violence carried out by the police, as well as neglect by police of physical or medical needs.[46] The traumatic effect of these experiences are due primarily to the imbalance of power between police and civilians, as well as the public's perception of police officers as having a prejudicial mindset. For example, when a police officer puts a gun to someone's head when that person has not threatened the officer, that person will be in fear for his/her life. When someone is stripped naked and subjected to a cavity search, s/he will interpret that act as a sexual assault. Experiencing racially motivated police harassment and violence can lead to chronic difficulty in achieving or maintaining good mental health and being prosocial.[47] Recognizing the role of the police in the perpetuation of racial trauma could be the first step toward healing for its victims. Case studies have revealed that individuals who experienced a posttraumatic reaction to police violence that was initially inadequately conceptualized (i.e., it was mistaken for anxiety, depression, oppositionality, etc.) had better outcomes when each situation was viewed more accurately as the outcome of racial trauma within a PTSD framework.[48]

Workplace Discrimination:

Workplace discrimination based on race, ethnicity, and gender can have multiple traumatic effects, some of which are described in the following case examples.

Carter and Forsyth presented the case of an African-American salesman who was treated in a demeaning manner by the store manager (i.e., he was denied time off, assigned to menial tasks, instructed to keep close tabs on black customers to make sure they did not steal anything).[49] After he filed several complaints against the store manager for racially discriminatory acts, the manager retaliated by firing him. As a result of these experiences, he exhibited symptoms of depression, anxiety, irritability, and hyperarousal while experiencing flashbacks and difficulties in his interpersonal relationships. These experiences were eventually conceptualized as reactions to race-based, trauma-related stress.

Williams and colleagues presented the case of a black woman employed as an IT professional who was invited to dinner by a white coworker during an overseas training.[43] During dinner, the coworker—a former soldier—bragged about torturing and killing people, making racist remarks along the way. He eventually made sexual advances toward her and threatened to kill her if she told anyone. Fearing for her life, she promised not to tell his story to anyone. She spent the rest of the night in her hotel room awake and holding a small knife while sitting in the bathroom where she had locked herself in and stayed until she was sure her "dinner companion" was on a plane back to the United States. She continued to fear for her life among her other white coworkers. A diagnosis of PTSD was made based on symptoms that included severe panic attacks and agoraphobia.

Muslim women who wear hijabs in the workplace are also targeted, experiencing verbal or sometimes physical assaults by colleagues who accuse them of being "terrorists."[50] The stress of such continual workplace harassment, punctuated by significant negative events (e.g., being passed over for a promotion), can contribute to traumatic reactions to future workplace stressors.

Community Violence:

Impoverished urban neighborhoods often present an environment in which residents experience an

increased threat of interpersonal trauma (e.g., from gang violence and armed robbery). Having fewer resources to buffer themselves against such assaults than individuals living in more economically stable communities, the residents of low-income communities may feel the need for greater vigilance, yet still react with increased anxiety to traumatic experiences.[51, 52] Given the recent dramatic rise in homicide rates in both white and black communities (due to a spike in the number of males aged 16 to 24 years, among other factors),[53, 54] coupled with a persistently dramatically higher unemployment rate for black males aged 16 to 24 years (e.g., 14.3% – 27.7% in second quarter of 2018) compared with whites in the same age groups (6.5% – 13.4% in second quarter of 2018),[55] the crime rate is higher in poor black communities. Being a victim of crime can result in traumatic stress reactions (e.g., flashbacks, hyperarousal, avoidance behavior) characteristic of PTSD; frequent exposure to crime simply increases the severity of the reaction. Individuals in such communities usually do not have the economic resources to move and may feel trapped in a perpetually stressful and traumatic environment. This sense of entrapment can exacerbate the severity of PTSD symptoms further. These factors collectively may contribute to the increased exhibition of symptoms of PTSD that is being seen in African-American children today.[56]

Distressing Medical and/or Childbirth Experiences:

Underrecognized causes of trauma include medical conditions and treatments. For example, childbirth—considered a "natural" and "normal" condition—actually poses a serious risk to the mother and infant. **Fear of injury or death to the mother or the infant can be traumatizing enough to result in a diagnosis of PTSD.**[57] When a traumatic response to pregnancy is potentiated by the actions—or inactions—of the medical providers—i.e., if their actions are interpreted by the pregnant woman as dehumanizing, disrespectful, or showing a lack of care—the sense of trauma is increased. Although the United States spends more money on prenatal care and childbirth than any other nation,[58] maternal and infant mortality rates lag far behind those of other developed countries. The main reason for this is poor labor and delivery outcomes in African-American communities, where maternal mortality is four times higher than for white women and infant mortality is twice that seen in other ethnic and racial groups.[59] Among other factors, racial differences in socioeconomic status, both real and presumed, contribute but only partially explain these differences.[60] For example, it is often assumed that a black woman seeking prenatal care is unmarried, multiparous, on welfare, and has poor health habits.[61] In turn, the black patient often believes the healthcare provider with this attitude is indifferent and disrespectful; as a result, she is less likely to be confident that the healthcare provider has her best interests at heart and wants to provide the best care.[61, 62] Patients who do not trust their providers are less likely to keep follow-up appointments for diagnostic screenings or adhere to treatment recommendations, which puts them at increased risk for adverse outcomes. Research has shown that providers are indeed more likely to have a negative bias against African-Americans that can result in poor pregnancy outcomes, particularly in low-income black communities.[63, 64]

Incarceration:

The trauma of incarceration has been likened to "being locked in cage [that] has a psychological effect upon everyone made to endure it" from which "no one leaves unscarred."[65] Incarceration can be so psychologically painful that it can result in posttraumatic stress reactions by the time the prisoner is released. Individuals who become incarcerated are more likely to have experienced both physical and sexual trauma during childhood (9.6%) than during adulthood (e.g., 3.7%).[65] The harsh, punitive environment of a prison, with its rigid rules and requirements for discipline, coupled with close proximity to violence, sexual victimization, and physical assaults, only serves to retraumatize these individuals.[66] Furthermore, exposure to trauma in prison is strongly associated with various behavioral problems (e.g., aggressiveness) and clinical symptoms (e.g., emotional dysregulation and hopelessness), which does not bode well for release.

Immigration Difficulties:

Immigration is a stressful and potentially traumatic experience involving complex emotional and physical challenges. In a study of Cuban refugees, for example, investigators found that the typical entrant had to traverse an average of 4.6 countries (*SD* = 2.70) before arriving in the United States;[67] they were often robbed, raped, or otherwise assaulted on the way and many of those traveling on boats witnessed or risked drowning. In a study

of foreign-born adolescents and their parents, Perreira and Ornelas found that 29% of adolescents and 34% of parents experienced physical assault, accidental injury, muggings, rape, etc. before reaching the United States;[68] others experienced severe illness, natural disasters, war, or persecution. Additional factors contributing to the risk for trauma consisted of premigration poverty; the clandestine nature of their entry into the United States; the loss of familial networks that can provide social, financial, and cultural support; and postmigration discrimination and violence. The challenges continue while they try to assimilate into a new cultural environment, learn a new language and societal norms, and accept jobs that they soon learn are associated with racial or ethnic stereotypes (e.g., a Latina working as a cleaner) and cause them to deal with a significant decrease in income, social status, and employability. These changes have been correlated with domestic violence and negative physical and mental health outcomes.[69, 70]

Deportation:

The effects of deportation are similarly to those of immigration, particularly if it is ordered after the family has established ties with new support networks in the "new" country. Witnessing the deportation of their parents can be extremely distressing and traumatizing for the children left behind. Allen, Cisneros, and Tellez investigated the effects of parental deportation on the psychological well-being (as reported by current caregivers) of the children who were left behind and found a significantly greater number of externalizing and internalizing problems in these children than in children whose parents were not deported or who were currently fighting deportation.[71] These problems were expected, given the traumatic nature of involuntary and often very sudden separation from one's parents and placement in the care of relatives or even strangers (i.e., foster families), particularly with no knowledge of what will become of the parents. These changes represent disruptive and destabilizing events that can reduce the sense of security in the family unit.

Trauma is Cumulative

Conceptualizing PTSD as the outcome of a single major traumatic event is inadequate. According to the "stress sensitization" hypothesis, exposure to prior traumatic events can increase the risk of PTSD on exposure to additional trauma in the future.[72, 73, 74] For individuals with multiple minority identities that are commonly stigmatized, the stressors and traumas related to each identity and the intersections among them can increase the risk for pathological responses exponentially.[75] Trauma may also accumulate in an intergenerational manner. Chronic exposure to environmental stressors associated with one's ethnoracial identity can trigger biological reactions that are passed along to subsequent generations,[76] causing them to develop an inheritable biological predisposition to respond to those stressors in a similar manner. Specifically, chronic exposure over several generations to stressors that induce racist trauma may be able to induce an epigenetic change in the levels of enzymes governing pathogenic processes involved in various depressive and anxiety disorders—including PTSD—and these changes may be inherited by later generations. The genes governing these enzymes may, in turn be activated by environmental factors.[77] Traumatic stress reactions in the offspring of Holocaust survivors may be an example of this process.[78] Based on this research, we believe that future studies will find that stress and trauma, based on racist experiences, can be cumulative and heritable.

The trauma induced by ongoing racism may be similar to the trauma triggered by bullying or sexual harassment and could result in PTSD. A study of Chinese-American immigrant youth found that chronic verbal and physical bullying, harassment, and/or other acts of discrimination (e.g., being ignored or socially ostracized) by school peers were perceived as stressful and overwhelming[79] and resulted in reduced self-esteem and academic achievement, along with doubt and confusion about the value of their ethnoracial identity. Similarly, chronic sexual harassment of women in the workplace can lead to pervasive feelings of powerlessness, vulnerability, and fear, as well as job dissatisfaction, reduced productivity, social withdrawal, and detachment from the organization.[80] These reactions have been linked with somatic complaints and an overall sense of being psychologically unwell. Importantly, these effects parallel outcomes commonly observed in victims of racial trauma.

In a similar vein, subtle forms of racism (i.e., racial microaggressions), particularly when experienced on a daily or almost daily basis, can have a traumatic effect on one's sense of psychological well-being and impair the individual's ability to cope with adversity.[52, 81] Racial microaggressions can be verbal or nonverbal, as well as intentional or unintentional, and are consistently

experienced by the targeted individual as subjugating, disturbing, demeaning, belittling, and, ultimately, dehumanizing.[82, 83] Exposure to microaggressions may disrupt self-regulatory processes involved in the control of aggressive or angry behaviors and result in social avoidance, dissociative symptoms, and anxiety—all of which are common in people with PTSD.[84]

Cultural and Historical Traumas

Because the effects of trauma may be inherited, it may be important to consider the impact of historical and cultural trauma on its survivors and on the generations that follow.

Research has shown that many of the Japanese Americans who were held in internment camps during World War II refuse to talk about their experiences in those camps.[85] This may reflect the horrifying and traumatic experiences they endured and may have been intended to serve as a means of avoiding reminders of the trauma; this is a characteristic of individuals with PTSD. It may also have been intended as a means of shielding their children from the pain they experienced. Ironically, the desire to shield future generations from their pain may have caused those generations to believe the worst about the experiences of their elders, and this can contribute to anxiety. Similarly, the descendants of Holocaust survivors have been shown to represent a larger proportion of individuals seeking and receiving psychiatric services than descendants of similar individuals who were not Holocaust victims,[86] perhaps as a result of the inheritable nature of trauma. Talking about the experiences has been associated with an increase in emotional distress in their descendants, however, indicating that having a relative who had been exposed to trauma is associated with deleterious effects.[85] These findings show that regardless of how survivors cope with war-based traumas, there tend to be negative intergenerational effects.

African-Americans report experiencing more discrimination during their lifetime than any other racial group in the United States.[31] The role of racism in the captivity, enslavement, and murder of their ancestors heightens the traumatic effect of racism they experience today, such that traumatic racism is experienced as a life-threatening event.[86] Such heightened trauma can accumulate over generations, thereby increasing the risk for PTSD in each subsequent generation.

Cultural losses remain relevant for many Native Americans in the United States. A majority of Native Americans think about these losses occasionally or frequently, and this may put them at increased risk for anxiety, mood disorders, and substance use disorders.[35] These cultural losses affect the people of the First Nations in Canada as well, where indigenous people are at an increased risk for trauma and twice as likely to complete suicide attempts as non-indigenous Canadians.[87] *Indian Residential Schools* (IRS; government mandated until 1996) disciplined children for expressing their indigenous culture (e.g., for speaking in their primary language), thereby fostering a sense of ethnic shame. Descendants of individuals who attended an IRS are at increased risk of suicidal ideation and suicide attempts. This risk is increased in individuals with two generations of IRS exposure.[87]

Case Examples

Racial Profiling of an African-American Male:

Kevin, a 25-year-old black man, was traveling with three friends to North Carolina to visit his family. The road took them through a rural area; soon, Kevin found himself lost in Virginia, driving through cotton and tobacco fields. A car ahead pulled out of the shadows and traveled in the opposite direction then made a quick U-turn, and was right behind Kevin's car. Suspecting that he was being followed, Kevin tried to evade the unknown vehicle. Emergency lights were turned on in the other vehicle and it soon became apparent that it was a police car. This made Kevin even more fearful, not only for his own life but also for his friends. He sped off and was successful at evading the police for miles—until he crashed into a hardware store.

Kevin was from Baltimore, Maryland, where the constitutional rights of black people are violated on a routine basis.[88] Keven had experienced a number of traumatic encounters with law enforcement personnel in the past. One of the most traumatizing experiences occurred when he was walking home from school alone. Two police officers approached him and began harassing him. One of the officers threatened to "put a hole" in him. Kevin was assaulted and pushed to the ground. He attempted to break his fall

by extending his hand, but he sustained an injury to his wrist that required surgery. After searching him, the officers stated they had the wrong person and let him go.

Kevin had also witnessed several troubling events in his community. For example, he saw his neighbor, who is black, shot by the police 17 times while unarmed. He was also troubled by the death of Freddie Gray, a 25-year-old black man who died after falling into a coma while riding in the back of a Baltimore police van in which he was being transported after being arrested for allegedly being in illegal possession of a knife. Kevin was also disturbed by the sudden death of several close relatives. His experiences caused him to be afraid that he would someday be shot by the police simply because he was black. Kevin now tries to stay out of plain sight and in public places to avoid police harassment. In fact, his primary motivation that night in Virginia was to drive until he found a place where other people were around, because he believed he would be less likely to be killed by the police in front of witnesses. After the high-speed chase and crashing his car, he was assessed by the first author (MTW) and found to be suffering from racial trauma.

Racial Harassment of an Asian-American Woman:

Amy is a 21-year-old, first-generation Japanese-American college student who sought mental health treatment with the second author (THWC) at a large, predominantly white public university in New England. Amy described an emotionally charged racist conflict with her white boyfriend's brother that had recently occurred in his parents' home during a Super Bowl party. She described the incident as "the straw that broke the camel's back." According to Amy, the racial tension in the room escalated quickly. While drinking, her boyfriend's brother made increasingly overtly racist comments about black football players, e.g., "These black players are only in here because they needed them to make up numbers." He used the "N-word" and hurled other derogatory racial epithets at players as they appeared on the television screen. Amy told him several times that she was hurt and angered by his behavior, only to face vicious verbal responses (e.g., "Shut up, you stupid b*! What the f*** do you know about football, you slant-eyed b****? Your people don't even f***ing play football!"). Amy felt threatened and powerless, because neither her boyfriend nor his parents stood up for her against the barrage of racist insults. She finally left the house in tears. A week later, her boyfriend broke up with her, and this exacerbated her sense of betrayal and abandonment.**

After these events, Amy reported feeling depressed and anxious and having difficulty sleeping. Despite being an achievement-oriented student until then, she lost her motivation to excel academically and her self-esteem declined even further. She also reported having nightmares about the incident (the primary cause of her sleep disturbances) and actively avoided her ex-boyfriend and his brother on campus. Reminders of the incident (e.g., seeing her younger sister wearing her ex-boyfriend's sweatshirt, which he had left at their home) triggered strong emotional reactions, including a "panic attack." After a careful assessment, she was diagnosed as experiencing racial trauma.

Assessment of PTSD in People of Color

Common validated measures of PTSD do not provide the opportunity to review incidents of racial trauma; therefore, no assumptions can be made concerning their validity for detecting race-based PTSD. **Only two validated self-report measures assess the patient for trauma due to discrimination and racist events: the *Race-Based Traumatic Stress Symptoms Scale* (RBTSSS) and the *Trauma Symptoms of Discrimination Scale* (TSDS).**[89, 90]

The RBTSSS is a comprehensive, 52-item assessment of racial trauma and stress. Each item is rated twice on a scale from 0 ("does not describe my reaction") to 4 ("this reaction would not go away") to indicate the patient's endorsement of symptoms immediately after the event versus recent symptoms and to determine if the patient knows if any of the symptoms were noticed by others. The RBTSSS includes a checklist of racism-related traumas and open-ended questions about the patient's traumatic experiences that can serve as an anchor for

questions about symptoms. This measure has seven scales: Depression, Anger, Physical Reactions, Avoidance, Intrusion, Hypervigilance/Arousal, and Low Self-Esteem. Scores are interpreted by converting the summed scale scores into T-scores. Research on the RBTSSS has been carried out in Asian, Latinx, and black populations, and it has been shown to be a reliable and valid measure of racial trauma.[89]

The TSDS was designed to evaluate anxiety-related symptoms of race-based trauma. This measure contains 21 items to assess the extent of distress resulting from discriminatory experiences. Rated on a scale from 1 ("never") to 4 ("often"), the total score consists of the sum of the patient's ratings. At the end of each measure, the patient can report the type of discriminatory activity that was experienced (i.e., racial/ethnic, sexual orientation, age, gender, religious, and other). Preliminary results have shown good convergence of validity and reliability when used with monoracial and biracial black college students. The TSDS is a fairly new assessment; more research is needed to determine its reliability and validity in various ethnoracial groups. However, it does show promise as a short and easily scored assessment tool.[90]

Williams and colleagues designed a survey—the *UConn Racial/Ethnic Stress and Trauma Survey*[91] UnRESTS)—to assess racial stress and trauma and help clinicians ask patients difficult questions about their experiences. The UnRESTS survey includes questions that can be used to assess the development of ethnoracial identity, a semi-structured interview to probe for a variety of racism-related experiences, and a checklist to determine whether the patient's racial trauma meets *DSM-5* criteria. The UnRESTS format is modeled after the *DSM-5* Cultural Formulation Interview,[1] which is available in both English and Spanish.

Minority Representations in Empirically Supported Treatments for PTSD

People of color may be more likely to underutilize mental health services or end treatment prematurely.[82, 92] Common reasons for disparities in treatment engagement include cultural taboos against mental health care, discriminatory actions experienced while attempting to access services, as well as language barriers and socioeconomic status.[93, 94, 95] People of color are consistently underrepresented in treatment studies, which further limits our understanding of treatment efficacy in these groups and differences across groups. US-based treatment efficacy studies were reviewed to determine whether minority groups were represented[96] in studies of *prolonged exposure* (PE), *cognitive processing therapy* (CPT), and *eye movement desensitization and reprocessing* (EMDR) in PTSD. The majority of participants across all studies were white (51.2%); however, black participants were oversampled compared with the black population in the United States (26.3% vs 12.7%, respectively) and Latinx and Asian participants were under-sampled (3% vs 17.8% and 0.8% vs 6.0%, respectively). Ethnoracial identity was unknown for 17% of participants because of the omission of demographic data or the combination of participants from different races into a "non-white" category.[96]

Research on the efficacy of PE therapy in people of color has been limited primarily to black (28.9%) and Latinx (3.5%) participants.[96] PTSD symptoms decrease with PE in ethnoracial minority groups at a rate similar to that seen in white participants,[97, 98] and there seems to be no significant difference in the continuation of treatment among these groups.[99] *Cognitive behavioral therapy* (CBT) may also be promising for people of color with PTSD. In studies in primarily African-American and non-Hispanic white-American populations, researchers found similar rates of treatment retention and symptom reduction in children who received trauma-focused CBT, imagery rehearsal, and nightmare management.[100, 101]

Some of these treatments had mixed results in people of color; in some studies, the differences in outcomes were not assessed. The EMDR studies were least likely to include Asian (0.0%), black (0.0%), and Latinx (0.8%) participants. CPT studies included the most Asian participants (2.5%) compared with the other PTSD treatment studies,[96] although several of the articles made a direct comparison between Black and White participants.[19, 102] In a sample of veterans accessing care through the Department of Veterans Affairs, white participants were more likely to have lower pretreatment PTSD symptom scores and greater degree of symptom reduction after treatment. Non-white participants also saw a significant reduction in symptom severity.[103] After controlling for socioeconomic status, researchers found that they were significantly more likely to remain in treatment than African-Americans (73% vs 45%, respectively), yet both groups experienced a reduction in PTSD symptoms.[19] In other studies,

treatment retention rates and decrease in symptomology was similar for white and non-white participants.[102, 104] These findings suggest that further research is needed to understand the efficacy of CPT in people of color.

The efficacy of *narrative exposure therapy* (NET) has been evaluated in numerous efficacy trials in participants from diverse ethnoracial groups with PTSD in refugee populations. Refugees, most of whom had insecure asylum status, had a high treatment retention rate with NET and demonstrated a significant reduction in PTSD symptoms that was sustained for 12 months after treatment.[18, 105, 106] The efficacy of this method has been evaluated in refugee children and adolescents; 75% of these patients no longer met the criteria for PTSD after 6 months of treatment. Similar improvements were observed in adult refugees.[20, 107]

Conclusion

In this lesson, we reviewed the symptomatology of PTSD and showed how racial trauma to people of color can elicit posttraumatic stress reactions. To do so, we provided a variety of examples of how race-related traumatic experiences can occur and the importance of being able to recognize and fastidiously assess patients for the occurrence of such experiences and their effects on the patient's mental health. **People of color with PTSD may present to medical appointments with primarily somatic complaints, which may not be recognized as PTSD, leading to a missed diagnosis and failure to provide appropriate treatment. Therefore, it is critical to evaluate patients thoroughly using a culturally competent PTSD assessment tool.**

Many clinicians feel uncomfortable discussing traumatic events associated with racism. It is imperative, however, for the clinician to set aside his or her emotions and assess the person of color objectively, rejecting stereotypes and providing a safe space to discuss race-based trauma. It is also important to let the patient know that you believe that the traumatic event being reported is, indeed, related to racism. Any attempt to provide an alternative explanation for the event could be seen as an attempt to invalidate the trauma or insinuate that the patient is at fault for the trauma. This, in turn, may traumatize the patient further. White clinicians can help establish a therapeutic alliance with each patient by setting aside their own feelings of guilt or defensiveness and not worry about their cultural competence. Clinicians of color should remain aware of their own internalized biases and avoid any countertransference.[108] Additional resources are available to identify treatments that are appropriate for race-related stress and trauma.[91, 108, 109] By acknowledging the nature and severity of each incident, carrying out an accurate assessment, and selecting an appropriate treatment for each patient with race-related PTSD, the clinician takes a critical step toward removing mental health disparities for all patients.

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Multiple-Choice Questions

45. According to the DSM-5, what are the core symptom clusters of PTSD?

A. Externalizing symptoms such as temper outbursts, mental and behavioral compulsions, cognitive and mood changes, heightened arousal

B. Intrusive symptoms such as flashbacks, avoidant behaviors, hallucinations, and heightened arousal

C. Intrusive symptoms such as flashbacks, avoidant behaviors, cognitive and mood changes, heightened arousal

D. Intrusive symptoms such as flashbacks, avoidant behaviors, cognitive and mood changes, impulse control difficulties, and suicidality

46. Certain experiences (e.g., racism) not covered under "Criterion A" in the DSM-5 can still cause trauma reactions, because:

A. They represent the culmination of chronic and stressful past experiences of discrimination that overwhelm the individual's ability to cope over time.

B. Racially motivated acts of violence, especially when committed by authority figures (e.g., the police, employers), can often be as traumatic as conventional index traumas (e.g., war, rape).

C. Cultural and historical traumas can have intergenerational effects, especially when institutional/structural forms of racism ensure the continued oppression of marginalized groups.

D. All of the above.

47. Community violence, distressing medical experiences, and immigration difficulties are common forms of racial trauma that may qualify for a diagnosis of PTSD in the DSM-5, because:

A. The individual may fear for the life/safety of self or loved ones during these experiences.

B. The individual experiences chronic physical health issues thereafter.

C. The individual fails to maintain employment thereafter.

D. All of the above.

48. Which of the following can be used to assess the severity of PTSD symptoms that occur specifically because of racial trauma to people of color?

A. *Beck Anxiety Inventory*

B. *Race-Based Traumatic Stress Symptom Scale*

C. *Beck Depressive Inventory—Second Edition*

D. *General Ethnic Discrimination Scale*

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Best Practices in CME

Assessing PTSD in Ethnic and Racial Minorities: Trauma and Racial Trauma

By Monnica T. Williams, PhD; Terence H. W. Ching;
Destiny M. B. Printz; Chad T. Wetterneck, PhD

ID#: L003415

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Ethnic and racially motivated traumatic events can cause PTSD in people of color. Unfortunately, this type of trauma is often not identified during clinical assessments. This lesson presents up-to-date methods of detecting racial trauma, validated self-report and clinician-administered PTSD assessment tools that are appropriate to use with persons of color, and guidelines for selecting the most appropriate treatment for patients with race trauma-related PTSD.

Key Point 1: Racial Trauma is Real and Cumulative

Racial trauma can be defined as a traumatic response to overt and covert race-related experiences that are collectively characterized as racism, and can include overt racial slurs and threats, police harassment, search, and assault, workplace discrimination, community violence, distressing medical and/or childbirth experiences, incarceration, immigration difficulties, and deportation. The trauma induced by ongoing racism, particularly when experienced on a daily or almost daily basis, can accumulate and overwhelm one's ability to cope with adversity.

Key Point 2: Racial Trauma Can Lead to PTSD

There is strong evidence that over time, racial trauma can result in significant psychological and physiological damage in people of color, thereby contributing to various forms of psychopathology, including PTSD.

Key Point 3: Racial Trauma Can Be Assessed Sensitively

The *Race-Based Traumatic Stress Symptoms Scale* (RBTSSS) and the Trauma Symptoms of Discrimination Scale (TSDS) are two validated self-report measures designed to assess the patient for trauma due to discrimination and racist events. Additionally, the *UConn Racial/Ethnic Stress and Trauma Survey* (UnRESTS) is modeled after the DSM-5 Cultural Formulation Interview, and is designed to assess racial stress and trauma and help clinicians ask difficult questions about patient experiences of ethnic and racial discrimination.

Key Point 4: Greater Ethnic and Racial Diversity in PTSD Treatment Studies is Needed

To better cater to the treatment needs of people of color, greater ethnic and racial diversity in PTSD treatment studies is needed. EMDR studies were least likely to include people of color.

Notes

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Cannabis: Medicine or Mayhem? Part II: Neurobiology and Health Impact of Marijuana

Drew W. Edwards, EdD, MS; Mark S. Gold, MD, DFASAM, DLFAPA

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

KEY WORDS: Cannabis Use Disorder • Marijuana • Δ-*9-tetrahydrocannabinol* (THC) • *Cannabidiol* (CBD) • Anandamide • Endocannabinoid • *Endocannabinoid system* (ECS) • Cannabinoid receptors • *2-Arachidonoylglycerol* (2-AG) • *N-arachidonylethanolamide* (AEA) • *gamma-aminobutyric acid* (GABA) • mesolimbic reward system • Co-Occurring mental illness.

LEARNING OBJECTIVES: After completing this educational activity, participants will be able to (1) demonstrate understanding of the endocannabinoid system, and its functional role in both central and peripheral systems; (2) differentiate the function of *Cannabinoid 1* (CB-1) from *Cannabinoid 2* (CB-2) receptors; and (3) describe risk factors and psychopathology associated with Δ-*9-tetrahydrocannabinol* (THC) consumption.

LESSON ABSTRACT: Marijuana is processed from female Cannabis Sativa plant. Its psychoactive ingredient—Δ-*9-tetrahydrocannabinol* (THC)—is the most commonly used psychoactive drug (behind alcohol) in the United Stated. Cannabis Sativa contains over 60 cannabinoids, of which THC and *cannabidiol* (CBD) are the most abundant. Both cannabinoids have been studied to determine their efficacy and safety as potential therapeutic agents.[1, 2] CBD is non-psychoactive, whereas THC is both psychoactive and addictive. The EC system includes 2 main receptor types. They are: CB_1 which involve the neurotransmission of THC throughout the *central nervous system* (CNS). The second receptor type is CB_2 which is predominately found in the brain's white matter and mediates activity of peripheral organs and tissues, and may play a significant role in the human immune system.[3]

At present, over 22 million Americans aged 12 years and older use marijuana regularly.[4] Of the 8000 Americans who will use an intoxicant for the first time today, 7000 will choose marijuana. Imaging studies and neurobiological investigations reveal neuroadaptive and functional deficits associated with marijuana use. Due to increased potency, THC in marijuana products are associated with neuroadaptive changes and psychopathology, particularly among early initiates, and persistent using adults.[5]

The life trajectory for early initiates (age 10–17) is wrought with academic failure, psychopathology, underemployment, multiple failed relationships and decreased life expectancy.[6] Conversely, CBD, a non-psychoactive constituent of cannabis is under scientific investigation for its therapeutic potential.

COMPETENCY AREAS: This lesson addresses the knowledge gaps regarding the function of the endocannabinoid system; the harmful effects of THC; and the potential therapeutic use of CBD.

Background

Over the past few decades, diverse opinions regarding the use, safety and medicinal value of cannabis has fueled great political, legal and social controversy. Medical professionals also have diverse opinions regarding the efficacy and safety of marijuana. In spite of well-established, empirically derived health and safety risks, the legalization of marijuana, via state level voter initiatives, in lieu of rigorous scientific inquiry is alarming. At the same time, the best available evidence has demonstrated that marijuana use is associated with neuroadaptive changes, psychopathology, physiological pathology, negative changes in life trajectory and decreased life expectancy.[7]

MUD is the second most cited reason for admission to substance abuse treatment programs behind alcohol.[2] Perceptions of harm are predictive of prevalence. Accordingly, prevalence of marijuana use has steadily increased while perceptions of harm have dropped steadily since the dawn of the new millennia.

The *Diagnostic and Statistical Manual of Psychiatric Disorders—5th Edition* (DSM-5)[8] describes MUD as a spectrum disorder that includes misuse, abuse, and addiction.

According to the DSM-5, current criteria for MUD include the following common symptoms:

- **Taking the drug in larger amounts or over a longer period than was intended by the user.**
- **A persistent desire to cut down or control one's use and unsuccessful efforts to do so.**
- **Failure to fulfill major obligations at work, school, or home as a result of marijuana use.**
- **Increased tolerance and/or occurrence of withdrawal symptoms during abstinence**

Prevalence

As we reported in part one, of this 3-part CME series, marijuana use is increasing in nearly all demographic groups in the United States. At present, 24 million Americans aged 12 years and older use marijuana, many on a daily basis.[9] Among the 8000 Americans who will use an intoxicant for the first time today (mostly teens and children), 7000 will choose marijuana.[2] Early initiation is associated with an increased risk for addiction and psychopathology.[8]

History and Pathophysiology of Cannabis:

In 1964, the psychoactive ingredient of Cannabis sativa, Δ-*9-tetrahydrocannabinol* (THC), was isolated by Israeli chemist Raphael Mecholaum.[10] In 1988, Devane, et al reported on the discovery of an endogenous ligand that activated the CB1 receptor[11] which led to the elucidation of an "endocannabinoid" system.[11] This *arachidonic acid moiety, N-arachidonylethanolamide* (AEA) was named "anandamide" for the Sanskrit word for "bliss" Anandamide a naturally occurring, lipophilic endocannabinoid that functions as a neurotransmitter. Its natural receptors are found throughout the brain and body. Over the past 3 decades endocannabinoids have been recognized as key mediators of numerous aspects of human pathophysiology and thus have emerged as among the most widespread and versatile signaling molecules ever discovered.[12]

A second cannabinoid receptor, CB2 was isolated in 1993 by Munro and colleagues[13] who reported that CB2 has a 44% amino acid identity with CB1, and thus represents a receptor subtype.

THC is believed to exert all of its effects on the brain via the CB1 receptor.[14] High densities of CB1 receptors are found in the cerebral cortex (especially frontal), basal ganglia, cerebellum, anterior cingulate cortex, and hippocampus. They are relatively absent in the brainstem nuclei. Stimulation of these receptors causes monoamine and amino acid neurotransmitters to be released. Endogenous ligands for CB1 receptors include anandamide and 2-arachidonylglycerol—the endocannabinoids.[15]

Both CB1 and CB2 cannabinoid receptors are members of the *G protein-coupled receptor* (GPCR) family that are pharmacologically well defined.[16] CB1-R receptors are abundant in the brain, specifically the mesocorticolimbic system, the spinal cord, and the peripheral neurons. CB1 receptors are particularly concentrated on both *gamma-aminobutyric acid* (GABA)–releasing neurons (inhibitory neurons) and glutaminergic-releasing neurons (excitatory). **Hence, activation of CB1-receptors leads to retrograde suppression of neurotransmitter release, which may be excitatory or inhibitory depending on the location in the brain.[17, 18] Like all drugs of abuse, THC activation of CB1-R cause presynaptic-inhibition**

of *gamma aminobutyric acid* (GABA), thus increasing dopaminergic surge in the nucleus accumbens, resulting in the mood-altering effects and the addictive potential of THC.

Additionally, distribution of CB1 receptors in the brain is consistent with the clinical effects elicited by the exogenous use of marijuana and FDA approved, synthesized cannabinoids. Of particular interest are short-term memory (hippocampus); anxiety and paranoia (amygdala); motivation, learning, attention (prefrontal cortex) and pain syndromes.[19]

CB1 is also important for energy balance. During fasting or starvation, anandamide and 2-AG levels increase in the limbic forebrain and, to a less significant extent, in the hypothalamus. Thus CB1-R activation increases food intake and effects energy metabolism through coordination of the mesolimbic reward system and the appetite control pathway in the hypothalamus.[20] This process also produces hyperplasia by increasing odor detection sensitivity in the olfactory bulb.[21]

CB2-R is encoded by the *Cannabinoid Receptor 2* (CNR2) gene. It is closely related to the CB1-R. The principal endogenous ligand for CB2-R is 2-arachidonoylglycerol (2-AG). CB2-R are found on the brains white matter, but are most abundant peripherally and function, in part, to mediate receptor signaling involved in immune and inflammatory reactions.

Current clinical trials have demonstrated efficacy and safety of CBD for treating children with a debilitating and rare seizure disorder, called Dravet syndrome, which is highly drug resistant and produces debilitating seizure activity in some children that is nearly continuous. Preliminary data revealed that over the course of the 14-week trial, children receiving CBD experience a median number of 5.9 convulsive seizures per month which is more than a 50% reduction prior to the use of CBD. When compared to matched controls receiving placebo, the median number of seizures went from 14.9 to 14.1 convulsions per month, which statistically, is no change in their seizure activity. In April 2018, a *U.S. Food and Drug Administration* (FDA) advisory panel unanimously recommended approval of the CBD medication Epidiolex to treat two debilitating seizure disorders—Dravet syndrome as mentioned, and Lennox-Gastaut syndrome.

The exact mechanism by which CBD produces its anticonvulsant effects is unknown. Researchers speculate that CBD may exert a cumulative anticonvulsant effect by modulating a number of endogenous systems including, but not limited to neuronal inhibition of synaptic and extrasynaptic GABA channels, modulation of intracellular calcium and possible anti-inflammatory effects. For the first time, there is now class 1 evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes.

CBDs potential as a safe and efficacious therapeutic is currently being evaluated for several clinical applications. Its potential for treating anxiety, neurogenic pain and inflammatory conditions have not stood up against rigorous, scientific scrutiny.

Until proven safe and effective, it's always best to assume some harm. We will explain CBD's potential as therapeutic for treating other conditions in greater detail, in Part 3 of this lesson.

Absorption and Intoxication of THC:

The route of administration determines the speed of absorption and the psychoactive effects of marijuana. When cannabis is smoked, the THC level in the blood rises quickly, reaching its maximum within a few minutes. If the drug is taken by mouth (e.g. infused into cookies, cake or candy), the maximum THC level is generally achieved between 2-6 hours (depending on whether the user is fasting, stomach content, etc.) The *maximum* subjective effect (the high) coincides with the blood level. The duration of intoxication is most dependent on the dose. If the dose is low, the effect lasts for a few hours if the drug smoked—and twice as long if it is eaten.[14]

The potency of marijuana has been increasing steadily over the past few decades (Figure 1).[22] This means exposure to much higher THC levels, increasing the risk of toxicity and adverse reactions. To wit, higher THC levels are associated with a dramatic increase of emergency room visits, especially in states where recreational use of THC is legal. Why? Like other commercially available products marijuana is marketed and sold to consumers at sanctioned commercial dispensaries. The convenience, product novelty and curiosity, conspire to increase sales of potent marijuana products.

Orally ingested cannabis products, known as "edibles" are becoming increasingly popular and marketed

and sold in various forms including beverages, candies, cookies, honey sticks, butter, and cooking oils.

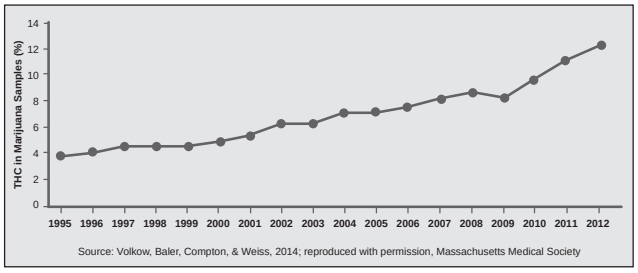
Cannabis oils are frequently homemade by experienced connoisseurs, using grain alcohol extraction or cooking cannabis in fatty substances to extract the oils for incorporation into food items, or smoked by adding to herbal marijuana. Cannabis-based oils are high in oleic acid, a known benefit of olive oil.[23]

Regrettably, the most popular edibles are the sweets and snacks, which are often packaged and marketed to resemble familiar food products, such as gummy bears, candy bars and baked goods. Edibles, which take longer to absorb and thus produce a higher sustained blood level of THC, are of particularly concern, especially for naïve users, unaware of the delayed psychoactive. These persons will consume larger doses in order to feel the effects sooner. Commercially available edibles can contain the highest levels of THC, resulting significant intoxication and impairment, and mortality via driving or when consumed by a toddler or young child.

> *"Marijuana-related (emergency department/urgent care) visits are of significant concern as patients are having significant acute medical or psychiatric symptoms requiring evaluation."*
>
> *—Dr. George Wang, pediatrician at the University of Colorado Anschutz Medical Campus in Aurora.*

Nationally, the number of pediatric marijuana intoxication cases reported to poison control centers has increased by 30% each year from 2005 to 2011. A 2016 study, published the *Journal of the American Medical Association* (JAMA) conducted at the University of Colorado revealed that emergency room visits in Colorado for children 9 and younger who consumed a THC product rose sharply after recreational marijuana use was legalized. Additionally, nearly twice as many children visited emergency departments in Colorado Children's Hospital in 2014 and 2015 as did in years prior to legalization of recreational use of marijuana. The researchers analyzed medical records from a children's hospital system and identified more than 4000 emergency visits related to marijuana use between 2005 and 2015. Moreover, annual poison-control cases increased five-fold during the same time period. Edible THC products accounted for nearly half of all accidental toxicity cases seen in hospitals. Intake evaluations revealed that the source of the THC was nearly always attributed to the child's parent.[24]

Figure 1:
Potency of *Tetrahydrocannabinol* (THC) in Marijuana seized by the DEA: 1995–2012:



Source: Volkow, Baler, Compton, & Weiss, 2014; reproduced with permission, Massachusetts Medical Society

Increased potency is associated with neuroadaptive changes, including tolerance, addiction and psychiatric disorders.[5] Although the blood level of THC falls rather quickly, partly because of conversion into metabolites and partly because of distribution into fatty tissue. Yet numerous studies have observed psychomotor impairment in persons 24–48 hours after smoking marijuana.[25]

Mechanism of Action:

Activation of cannabinoid receptors by exogenous THC affects serotonin release, increases catecholamines, specifically dopamine volume in the midbrain via inhibition of GABA. THC also inhibits parasympathetic activity, and prostaglandin biosynthesis.

Metabolism and Elimination of THC:

Below is a pharmacokinetic summary.

- **Absorption: 10–20% (inhaled); 1–10% (PO)**
- **Onset of action: 6–12 min (inhaled); 30–120 min (PO)**
- **Peak effect: 20–30 min (inhaled); 2–3 hours (PO)**
- **Toxic dose (THC): 15 mg/kg; Lethal dose: 30 mg/kg**
- **Duration of effect: 2–6 hours**

- **Volume of Distribution: 10 L/kg (increases with chronic use)**
- **Protein Bound: 97–99%**

After intake, THC undergoes metabolism via the cytochrome P450 (CYP450) enzyme system into an active compound, 11-hydroxy-THC (11-OH-THC), which is further metabolized into an inactive metabolite (8-11-DiOH-THC) and then, to a highly active metabolite (11-OH-delta-9-THC). The half-life of THC is approximately 4 hours. The long life of the active metabolite is explained by the incorporation of the compound in lipid storage depots. Thirty to 60% of THC, in all forms, is excreted in feces; the remaining amount is excreted in urine.

Within 5 days, nearly 90% of THC is eliminated from the body. However, the remaining 10% is stored in adipose tissue, the brain and gonads. Studies using simulated driving and flying situations have shown that the use of cannabis has a profound effect on estimations of time and distance and causes impairment of attention, executive function and short-term memory. These effects are still discernible 24-48 hours after use of the drug. A linear relationship exists between level of impairment and serum/saliva THC level in psychomotor function necessary for driving, such as perceptual motor control, impulsivity, and cognitive function. A double-blind, placebo-controlled, randomized study showed that therapeutic doses of medicinal THC (dronabinol) impairs driving ability in healthy adults to the same extent as alcohol at blood levels of 0.5-1 mg/mL. Accordingly, the ability to drive (or fly an aircraft) is impaired with even small doses of THC.[26]

Adverse Interaction:

There is growing concern over potential adverse interaction with the CB1 antagonist medication *Rimonaban*t, used for weight loss. Meta-analysis published in Lancet suggest that daily use of rimonabant (20 mg per day) increases the risk of adverse psychiatric events (i.e., depressed mood and anxiety).[27] These data, plus the FDA finding of increased risk of suicide during treatment with rimonabant, should alert physicians, especially when addressing obesity or depressed or anxious mood.

Tolerance:

Repeated use over days to weeks induces considerable tolerance to the behavioral and psychological effects of cannabis. Several studies have noted partial tolerance to its effect on mood, memory, motor coordination, sleep, brain wave activity, blood pressure, temperature, and nausea. The rate of tolerance depends on the dose and frequency of administration. The casual cannabis user experiences more impairment in cognitive and psychomotor function to a particular acute dose than heavier, chronic users. The desired recreational high from cannabis also diminishes with use, prompting many users to escalate the dose.

Pharmacologically the downregulation of the CB1 receptor from chronic use has been identified in several regions of the rat brain. No correlations have been made in human physiology.

Cannabis Use Disorder:

Cannabis use disorder is defined by DSM-5 as the following:

- **A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-month period:**
- **Cannabis is often taken in larger amounts or over a longer period than was intended.**
- **There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.**
- **A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.**
- **Craving, or a strong desire or urge to use cannabis.**
- **Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.**
- **Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.**

- **Important social, occupational, or recreational activities are given up or reduced because of cannabis use.**
- **Recurrent cannabis use in situations in which it is physically hazardous.**
- **Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.**
- **Tolerance, as defined by either a (1) need for markedly increased cannabis to achieve intoxication or desired effect or (2) markedly diminished effect with continued use of the same amount of the substance.**
- **Withdrawal, as manifested by either (1) the characteristic withdrawal syndrome for cannabis or (2) cannabis is taken to relieve or avoid withdrawal symptoms**

Brain Reward Usurped by THC = Addiction:

The brain's reward system consists of numerous brain structures which organize to regulate and mediate mood and behavior, germane for survival. The reward systems include, the *ventral tegmental area* (VTA), *medial forebrain bundle* (MFB), *nucleus accumbens* (NAc), *ventral pallidum* (VP) and *prefrontal cortex* (PFC). The reward pathway AKA, the mesolimbic dopaminergic pathway begins at the VTA, where central DA is synthesized, ascending to the NAc, which releases dopamine in response to the specific drug and delivery system. DA acts on DA 1 or DA 2 receptors to either stimulate (D1) or inhibit (D2) their action. The reward pathway terminates in the PFC, which normally functions to mediate and inhibit primitive hedonic survival signals from the midbrain. All drugs of abuse usurp the reward system by providing salience for addictive substance by releasing excess dopamine, and concurrently muting the inhibitory function of the PFC, which results in loss of behavioral control.

Reward Muting in Chronic Users

Marijuana abusers show lower positive and higher negative emotionality scores than do age matched controls. This is consistent with clinical findings of lower reward sensitivity and motivation and, heightened stress response and irritability. In novel research using *Positron emission tomography* (PET scan) conducted by Volkow, et al investigators compared the brain's reactivity in marijuana abusers vs. age matched controls during a *methylphenidate* (MP; Concerta, Daytrana, Ritalin) challenge. Marijuana abusers were observed to under respond to MP, evidenced by decreases in striatal DA distribution volumes. These deficits, while not absolutely conclusive, reflect a downstream postsynaptic effect of reward salience in the ventral striatum region, which contribute to a flattened and negative emotional state and compensatory drug seeking behavior.

We now understand that the ECS contributes to the regulation of "normophysiologic" central DA reward that includes hedonic drives, e.g., food intake, hydration, sexual activity, motivation and new learning. THC like all drugs of abuse of activate the same brain reward system, and increases DA levels, primarily by inhibiting GABA.[28] Moreover, long-term use of THC is associated with blunting of the dopamine system and reduction in reward salience and motivation leading to compensatory drug seeking behaviors.[29]

Cannabis Withdrawal

DSM-5 criteria for cannabis withdrawal is described for frequent and persistent cannabis users, e.g., daily or nearly daily users (3-5 times per week) over a period of several months.

- **Three or more of the following signs and symptoms develop within approximately 1 week after cessation of heavy, prolonged use:**
  - **— Irritability, anger or aggression**
  - **— Nervousness or anxiety**
  - **— Sleep difficulty (i.e., insomnia, disturbing dreams)**
  - **— Decreased appetite or weight loss**
  - **— Restlessness**
  - **— Depressed mood**

— **At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache**

- **The signs or symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.**
- **The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.[8]**

Health Risks:

The adverse health effects of marijuana use are statistically linked to several significant adverse effects and disease.

Cardiovascular effects associated with marijuana use include:

- **Naive users may experience a sudden 20–100% rise in heart rate, lasting up to 2–3 hours.[30]**
- **Cardiac output increases by as much as 30%, and cardiac oxygen demand is also increased and peripheral vasodilatation resulting in postural hypotension, dizziness or syncope.[31]**
- **Tolerance to these effects can develop within a few days of use**
- **Naive users can experience angina; in addition, users with preexisting coronary artery disease or cerebrovascular disease may experience myocardial infarctions, congestive heart failure, and strokes.[32]**

Reproductive Effects include the following.

- **THC alters the normal ovulatory cycle by decreasing follicle stimulating hormone, luteinizing hormone, and prolactin and impairing sex hormone secretion. THC also crosses the placenta and accumulates in breast milk.[33]**
- **THC impairs placental development and homeostasis, fetal nourishment and gas exchange. For this reason, it is implicated in low birth weight, growth restriction, pre-eclampsia, spontaneous miscarriage, and stillbirth.[34]**
- **A growing body of evidence suggests permanent, though subtle, effects on memory, informational processing, and executive functions in the offspring of women who use cannabis during pregnancy.[35]**
- **Children younger than 1 week of age born to mothers who used cannabis during pregnancy had increased incidence of tremors and staring. Children of chronic users (>5 joints per wk.) were found to have lower verbal and memory scores at age 2 years.[35]**

Cognitive Deficits:

In the short term, marijuana use impairs important cognitive functions such as attention, memory, learning motivation and decision-making. Those effects can last for days after the subjective "high" wears off.[36] Short-term memory is impaired even after small doses in both naive and experienced users. The deficits appear to be in acquisition of memory, which may result from an attentional deficit, combined with the inability to filter out irrelevant information, information retrieval and the intrusion of extraneous thoughts. The best available evidence suggests that marijuana impairs critical thinking and memory functions during acute exposure and that these deficits persist for days after intoxication. In addition, long-term studies showed that regular marijuana use during the early teen years is associated with robust neuroadaptation, cognitive deficits including lower IQ scores persisting into adulthood, even when the user stopped smoking marijuana in early adulthood.[5]

CB-1 receptors are most prevalent in the prefrontal cortex, left ventral striatum, hippocampus, amygdala, basal ganglia, and cerebellum. These brain regions undergo prominent developmental changes throughout childhood and myelination during adolescence, and thus may be particularly susceptible to the adverse cognitive effects of marijuana. Adolescents who use marijuana regularly have increased volumes in the cerebellum, possibly from failure to prune synapses effectively.[37] These adolescent marijuana users also show increased brain processing effort on fMRI during an inhibition tasks and task performance,

even after 28 days of abstinence Taken together, there is compelling evidence that chronic increases in stimulation of the brain's cannabinoid system can lead to morphologic and physiologic changes especially during adolescence.[38]

Marijuana Use Lowers IQ:

A recent NIDA-supported a longitudinal study conducted by researchers from Duke University. The team collected data from the Dunedin Multidisciplinary Health and Development Study that has followed 1,000 New Zealanders born in 1972. Participants were interviewed at 18, 21, 26, 32 and 38 and also underwent neuropsychological testing at ages 13 and 38.[39] The results were shocking. Persistent marijuana use was linked to a decline in IQ, even after controlling for educational differences and other covariates. The most persistent users, experienced a drop in neuropsychological functioning equivalent to about six IQ points.[40] Participants with more persistent cannabis dependence generally showed greater neuropsychological impairment.[41] Inspection of the means suggests that the highest impairment was found in domains of executive functioning and processing speed. To test whether impairment was relatively greater for certain domains, cannabis-associated neuropsychological impairment was compared across the four *Wechsler Adult Intelligence Scale-IV* (WAIS-IV) indexes (i.e., working memory index, processing speed index, perceptual reasoning index, and verbal comprehension index), which share psychometric properties. The results showed that associations between persistent cannabis dependence and the four WAIS-IV indexes could be equated without a deterioration in model fit ($\Delta\chi 2 = 2.13$, df = 3, $P = 0.55$). This suggests that impairment was not significantly different across neuropsychological domains.

Psychiatric Risks:

Recent well powered studies have shown a statistically significant causal association between marijuana use and mental illness.[42] Heavy marijuana use during adolescence or early adulthood is associated with a dismal set of life outcomes including poor school performance, higher dropout rates, mental illness, increased welfare dependence, greater unemployment and lower life satisfaction.

Marijuana use in young women is associated with a fivefold plus, increase of reporting states of depression and anxiety, after adjusting for intercurrent use of other substances (odds ratio 5.6, 95% confidence interval 2.6 to 12). Teenagers who used marijuana at least weekly have approximately a twofold increase for developing depression and anxiety (1.9, 1.1 to 3.3) after adjustment for baseline confounders.[43]

Numerous lines of evidence suggest a correlation between cannabis consumption and a variety of psychiatric conditions, including *cannabis-induced psychosis* (CIP). While it can be difficult to differentiate CIP from other psychoses, CIP holds distinguishing characteristics, which may aid in its diagnosis. Features of CIP are sudden onset of mood lability and paranoid symptoms, usually within 1 week of use but often as early as 24 hours after use of high potency THC, or increased quantity of cannabis consumption often precipitated from toxicity after consumption of more than 2 g/d).[44] Criteria for CIP must exclude primary psychosis, and symptoms should be in excess of expected intoxication and withdrawal effects. Characteristic of CIP, distinguishing it from typical psychosis, is an awareness of the clinical condition, greater disease insight, and the ability to identify symptoms as a manifestation of substance use or mental illness. Rapidly declining positive symptoms of schizophrenia is another distinctive factor of CIP.[45]

The distribution of the *endocannabinoid system* (CB1) in the brain is not unlike the areas also implicated in psychoses, particularly schizophrenia. Moreover, the complexity and involvement of this system with other neurotransmitters, including dopamine, GABA and glutamatergic systems are also implicated in the development of psychotic illness.[46]

Mortality:

Eighteen to 19-year-old males, who are heavy cannabis users, are 40% more likely to die by age 60 than their peers with no history of cannabis use. Published in the *American Journal of Psychiatry*. Lead author, Edison Manrique-Garcia, MD, PhD, commented. "This is the first study to show that mortality rate among heavy cannabis users in adolescence is significantly higher than that of individuals who never used cannabis." A form of cardiovascular disease is associated with these findings. The study also revealed that death from either accidental or deliberate injury, were also among the top causes of death in heavy cannabis users.[47]

Summary

The increased prevalence of marijuana use, combined with the increased potency of marijuana products cause neuroadaptation through the degradation of neuronal circuitry in areas of the brain critical for learning, focus motivation and reward.[48] The onset of psychiatric symptoms and emergencies—including hypertension, tachycardia, panic attacks, severe anxiety, hallucination, dissociative episodes, depression, suicidality, psychosis, and drug-induced schizophrenia—has increased in lockstep with the use of the highly potent marijuana. More research and prevention measures to delay initiation,[49] and reduce frequent and heavy use are needed.[50]

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Multiple-Choice Questions

49. According to DSM-5, which of the following is not a criteria for marijuana use disorder?

A. Previous or concurrent psychiatric disorder.

B. Failure to fulfill major obligations at work, school, or home as a result of marijuana use.

C. Taking the drug in larger amounts or over a longer period than was intended by the user.

D. Inability to cut down or control use.

50. Regarding the action of CB-1 receptors in the brain, which statement is true?

A. THC binding to CB-1 receptors play an important role in mediating the human immune response.

B. Activation of CB1-receptors leads to retrograde suppression of neurotransmitter release, which may be excitatory or inhibitory depending on the location in the brain

C. CB1-R activation decreases food intake and disrupts energy metabolism through activation of the appetite control pathway in the hypothalamus.

D. Central CB-receptor volume is mostly mediated though the release of hepatic enzymes, particularly acetaldehyde.

51. According to the best evidence on metabolism and elimination of smoked THC, which statement is most accurate?

A. After 30 days, 85% of the THC is eliminated from the body.

B. Because THC is lipophilic research has not shown which metabolites are eliminated and which are stored adipose tissue.

C. After 5 days, 90% of THC is eliminated from the body via the hepatic CYP-450 enzyme system.

D. THC is hydrophilic and therefore completed eliminated by the hepatic CYP-450 enzymes system within 72 hours.

52. Regarding the effect of marijuana use on cognition, which statement(s) is/are true?

A. Early initiation correlates highly with cognitive deficits.

B. Marijuana use during adolescence is associated with a decline in IQ later in life.

C. Acute and chronic intoxication is associated with deficits in short term memory.

D. All the above

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Best Practices in CME

Cannabis: Medicine or Mayhem?
Part II: Neurobiology and Health Impact of Marijuana

By Drew W. Edwards, EdD, MS; Mark S. Gold, MD, DFASAM, DLFAPA

ID#: L003416

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 is designed to help clinicians understand the pathophysiology and risks associated with marijuana use and the potential medicinal benefits of cannabidiol.

Key Point 1: Identification

The *endocannabinoids* (EC) and the EC system were not elucidated until 1992. At present, the best available evidence reveals a ubiquitous EC system that is involved in the mediation of numerous physiological and cognitive and emotional functions. EC1 receptors are primary involved with the CNS as EC2 receptors mediate physiological functions including human immune response. THC binds selective to CB1 receptors throughout the brain and like all drugs of abuse, THC activates the dopaminergic activity along the reward pathway in the midbrain and prefrontal cortex by way of GABA inhibition.

Key Point 2: Risk Factors of Early Marijuana Use

Early initiation of marijuana and persistent use are associated with numerous cognitive deficits including a drop in IQ equaling ½ standard deviation. Other risk factors include addiction, depression, anxiety disorder, psychosis, schizophrenia, suicidality, academic failure and underachievement, unemployment, and multiple failed significant relationships and premature death. Pediatricians and primary care physicians, and school health professionals should aquatint themselves with knowledge of these risk factors including comorbid psychiatric disease and educate and screen for signs and symptoms of early initiations.

Key Point 3: Marijuana Use in Pregnancy

Woman of childbearing age should be educated regarding the risks associated with THC exposure during pregnancy and early postnatal development. If signs of marijuana or any substances use disorder are suspected during gestation, a timely referral to a high-risk pregnancy obstetrician is warranted. If postpartum substance abuse by either parent is suspected an experienced addiction professional should be consulted, as time is of the essence.

Key Point 4: Need for Education

Pediatricians and primary care physicians should be educated regarding the risks associated with early THC exposure and persistent marijuana use and be prepared to educate their patients regarding the individual risk factors and know where and how to refer a patient with a MUD.

Key Point 5: Assessment

Clinicians who provide clinical assessment for MUDs should be aware of the high co-occurring prevalence of psychiatric disease and respond accordingly. Individualized, patient centered care requires a working knowledge of specific treatment modalities, local and regional centers and contacts for consultation and referral to addiction and psychiatric experts.

Key Point 6: Informed Consent

When professional addiction treatment is indicated, the clinician should educate the patient regarding the risks and benefits of treatment. The referring clinicians can and offer support and assist in arranging treatment and provide any records necessary, via patient consent.

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Management of Treatment-Resistant Depression in Late Life

Burhan Khan; Anam Zehra, MBBS; Asim Shah, MD; Awais Aftab, MD

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

KEY WORDS: Geriatric psychiatry • Major Depressive Disorder • Treatment-Resistant Depression

LEARNING OBJECTIVES: Upon reading this lesson, clinicians will be able to understand the prevalence and burden of depression and treatment-resistant depression in the geriatric population; appropriately assess for the diagnostic variables related to *treatment-resistant depression* (TRD) in geriatric patients; and evaluate the available treatment options for TRD in late life on the basis of the research evidence.

LESSON ABSTRACT: TRD in late life is common but poorly studied. This condition requires special considerations; thus, this paper presents an outline of the clinical assessment and management of TRD in geriatric subjects. It focuses on the appropriate assessment of diagnostic variables related to treatment resistance and evaluates available treatment options for TRD in late life on the basis of the research evidence. TRD is typically defined as an inadequate response to at least two antidepressant trials of adequate dose and duration; however, the definitions used in clinical research studies have varied. Several diagnostic variables are involved in late-life TRD that require detailed consideration and assessment, including incipient dementia, comorbid medical conditions, psychotic features, treatment tolerance and adherence, treatment duration, and antidepressant selection. Pharmacological strategies for late-life TRD include switching medications (to serotonin or norepinephrine reuptake inhibitors, or selegiline) and augmenting treatment (with lithium, second-generation antipsychotics, or thyroid hormones). Augmentation with either lithium or aripiprazole currently has the best evidence-based support; however, insufficient research exists on late-life TRD. Ketamine could emerge as a future treatment option for this patient population. Nonpharmacological strategies, including psychotherapy, for late-life TRD also remain understudied, but electroconvulsive therapy is widely considered to be an effective strategy. There is insufficient evidence to recommend continued augmentation treatment in late-life subjects with TRD following remission of depression with acute treatment, but the indirect evidence suggests that continued augmentation treatment may be helpful in some cases.

COMPETENCY AREAS: This lesson addresses gaps in the knowledge regarding the care of geriatric patients with TRD. Many psychiatrists lack knowledge and appreciation of the burden of TRD in older adults, the diagnostic variables involved in the assessment of treatment resistance, and the evidence-based treatment strategies available to clinicians. Upon completing this lesson, readers will have a better understanding of treatment resistance in late-life depression, the assessment of treatment resistance, and appropriate pharmacological and non-pharmacological strategies for the treatment of TRD in late life.

Introduction

The lifetime prevalence of *major depressive disorder* (MDD) globally is reported to be 12%;[1] however, the lifetime prevalence of MDD in adults in the United States is 17%,[2] with a 12-month prevalence of approximately 7%.[3] It is projected that by 2030, the greatest burden of mental illnesses in high-income countries[4] will come from depression. The prevalence of major depression in adults older than 55 is approximately 2%, which is lower than that in the general adult population; despite the lower prevalence of major depression, clinically significant depressive symptoms may be experienced by as many as 14%[5] of older adults. The prevalence of depressive symptoms increases in the very old (more than 85 years old) in hospitals and nursing homes.[5] Providing treatment for geriatric patients requires additional considerations given multiple medical comorbidities, the possibility of cognitive impairment, and resulting functional disability from the disorder. Depression is often undiagnosed in the geriatric population. Few clinical studies include subjects from this age group. Specifically, *treatment-resistant depression* (TRD), depression that has not responded to standard antidepressant therapy, remains poorly studied in the elderly. The results of previous studies suggest that remission rates with *selective serotonin reuptake inhibitor* (SSRI) or *serotonin–norepinephrine reuptake inhibitor* (SNRI) monotherapy range from 28 to 44%.[6]

Because TRD in late life requires special considerations, this paper presents an outline of the clinical assessment and management of TRD in geriatric subjects. It focuses on the appropriate assessment of diagnostic variables related to treatment resistance and evaluates available treatment options for TRD in late life on the basis of the research evidence.

Assessment and Diagnosis

In clinical practice, TRD is typically defined as an inadequate response to at least two antidepressant trials of adequate dose and duration;[7] however, a review of the literature suggests that the definition of TRD varies widely. Multiple different definitions of TRD have been used in clinical trials for late life depression. These definitions include: (1) failure to respond to at least one antidepressant, (2) failure to respond to at least two antidepressants, and (3) failure to respond to a combination of an antidepressant and a psychological therapy.[8]

At present, no validated biological markers for depression exist for clinical use in the diagnosis, prediction, or management of TRD, although this remains an active area of research. Vascular depression is a subtype of depression in the geriatric population characterized by small-vessel ischemia and subcortical white matter hyperintensities identified via magnetic resonance imaging; it is considered to be poorly responsive to antidepressants compared to non-vascular depression.[9] The rating scales for measuring the severity of depressive symptoms, whether self-reported, such as the *Geriatric Depression Scale* and the *Patient Health Questionnaire* (PHQ-9), or clinician-administered, such as the *Hamilton Depression Rating Scale* (HDRS), can be clinically helpful in identifying and monitoring treatment resistance.[10, 11, 12]

Older depressed individuals may not present with depressed mood but may present instead with physical symptoms, such as fatigue, weight loss, pain, memory complaints, social withdrawal, self-care issues, and refusal to eat, drink, or take medication. Patients might not have insights about these symptoms; therefore, clinicians must be vigilant in identifying the symptoms and accurately diagnosing depression if it is present.[13]

The tendency of geriatric patients to under-report their symptoms may result in part from memory loss or other cognitive deficits that may or may not be secondary to depression, thereby necessitating a thorough clinical interview in conjunction with gathering collateral information from family members and caretakers.[14]

Table 1:
Assessment of TRD in Late Life

- Assess for comorbid medical issues, such as Parkinson's disease and chronic pain syndromes that might be causing or contributing to depression.
- Screen for thyroid abnormalities.
- Conduct a thorough cognitive assessment to rule out the presence of mild cognitive impairment or dementia.
- Review the medication list, and check for side effects of medications, such as high-dose steroids, that might predispose to depression.
- Check for medication adherence.
- Assess for psychotic features.
- Assess for undiagnosed or untreated comorbid psychiatric disorders, such as obsessive-compulsive disorder, post-traumatic stress disorder, or personality disorders.

- Assess for bipolarity of mood symptoms to rule out bipolar disorder. Bipolar depression responds poorly to standard antidepressants.
- Determine whether prior medication trials were of adequate dose and duration.

Diagnostic Variables Involved in Assessment of Late-Life TRD

Atypical depressive symptoms, cognitive impairment, and comorbid medical diseases can present challenges for the diagnosis and management of depression in the elderly.[15] This section outlines the necessary considerations when dealing with an elderly depressed patient responding poorly to antidepressants. These factors are detailed in Mulsant and Pollock's review paper.[15]

Incipient Dementia:

Considering the overlap in symptomatology, the relationship between dementia and depression is quite complicated. There is a 10–30% prevalence rate of depressive symptoms in patients with Alzheimer's disease.[16] Depression is also among the potential signs of dementia onset.[17] Even with successful treatment, patients with Alzheimer's may be labeled treatment resistant because of symptoms such as motor retardation, sleep disturbances, and cognitive impairment, which may result not from the depression but from the underlying dementia.

Comorbid Medical Conditions:

Medical illnesses in late life are commonly associated with the presence of depression; thus, the treatment of these illnesses becomes an important part of the management of depression. Medical disorders such as Parkinson's disease, stroke, heart disease, arthritis, thyroid disease, and cancer are well recognized as being associated with a higher risk of depression,[18, 19] and depressive symptoms might not respond to antidepressant therapy until the associated medical condition has been appropriately managed.

Folate or *methylcobalamin* (Vitamin B12) deficiency can also be associated with depressive symptoms, an association which often goes unrecognized.[15] These vitamins are involved in rate-limiting steps in the synthesis of catecholamines, which play a significant role in depression.[20] Several studies have linked folate deficiency to poor antidepressant response; however, fewer studies have addressed the role of Vitamin B12.[21] The measurement of folate and Vitamin B12 must be considered in the management of late-life TRD because an untreated deficiency may undermine patient response to treatment.

Psychotic Features in Late-Life Depression:

Older patients with depression are more likely than younger patients to display psychotic symptoms.[22] Psychotic symptoms are present in 25–50% of older patients with depression considered severe enough to require hospitalization.[23] While some studies have shown improvements in psychotic depression upon administration of antidepressants alone, antidepressants in combination with antipsychotic agents are preferred if psychotic symptoms are present.[24, 25, 26] *Electroconvulsive therapy* (ECT) may also be used as a treatment option for depression with psychotic features.

Treatment Tolerance and Adherence:

Non-adherence is a major contributor to poor outcomes in depression treatment.[15] The stigma associated with mental illness, poor knowledge of depression and its treatment, negativity toward drug therapy, lack of family support, and cost of medications may all contribute to medication non-adherence.[27] The inability to tolerate one or more antidepressants at the therapeutic dosage also results in inadequate therapy.[28] Somatic symptoms have also been associated with poor outcomes because of under-treatment.[29] Abdominal, urinary, and cardiovascular symptoms, which are common in geriatric depression, can be misevaluated as medication side effects, leading to premature discontinuation of medications.[30] Patients and their families should be counseled on the possibility of side effects and/or the worsening of somatic complaints during the initial treatment phase. They should also be informed about the probable resolution of these issues in the later stages of treatment.[15]

Significant adverse effects can make it difficult in practice to determine the effectiveness of an antidepressant trial. Patients may consider an antidepressant to have been ineffective for their depression, but this judgment may have been distorted by concomitant side-effects (particularly distressing side-effects such as sleep disturbance, anxiety, sexual dysfunction or cognitive impairment). Also, these side-effects are often associated

with non-adherence. Therefore, it is important to ensure that a depressive episode labeled as 'treatment resistance' is not simply labeled based on antidepressant trials which were failed primarily due to side-effects.

Fewer patients are able to complete adequate trials of the more sedating antidepressants, such as *trazodone* (Desyrel).[31] Geriatric patients taking *tricyclic antidepressants* (TCAs) are particularly susceptible to anticholinergic side effects, which can potentially result in fecal impaction, cardiac conduction defects, cognitive impairment, and hip fractures.[32] In contrast, SSRIs are less likely to be associated with side effects;[33] **Regarding SSRIs, *paroxetine* (Paxil, Pexeva) should be avoided for the geriatric population because of its stronger anticholinergic and sedating effects and the possibility of interactions with other drugs.** For these reasons, paroxetine has been included in the American Geriatrics Society 2015 updated Beer's Criteria as a potentially inappropriate medication for use in older adults.[34] Fluoxetine is also considered a less attractive choice for the treatment of geriatric patients because it has a long half-life, active metabolites, and a propensity to cause drug-drug interactions.[15]

Treatment Duration:

Clinical trials in the adult population have typically considered 6–8 weeks of antidepressant therapy sufficient to determine a response.[31] However, many geriatric patients may require a longer treatment duration to achieve an adequate response.[15, 32] A study observing the trajectories of symptomatic improvements in depressed geriatric patients treated with nortriptyline reported large individual variations.[33] Some patients exhibited a rapid resolution of symptoms (2–3 weeks); however, for others, improvement occurred only after several weeks. In another study, nearly half of the older depressed patients not responding after 7 weeks to treatment with either *nortriptyline* (Pamelor) or *phenelzine* (Nardil) responded when the trial was extended to 9 weeks.[34] In a study comparing *sertraline* (Zoloft) to *imipramine* (Tofranil) for treating dysthymia, the maximal treatment duration was as much as 12 weeks or more.[35] Therefore, older patients who fail to respond to antidepressant medications may actually be slow responders, requiring trials of 8, 10, or even 12 weeks. Longer trials may also be needed for patients previously failing to respond to shorter trials who exhibit comorbid anxiety and depressive symptoms.[15, 36]

Treatment Options for Late-Life TRD

Once late-life TRD has been appropriately assessed and any contributing factors have been addressed, persistent depression requires treatment, which can be pharmacological or non-pharmacological. This section briefly reviews the late-life TRD treatment options that have been studied in clinical trials.

Pharmacological Strategies:

Lithium Augmentation

Prior to investigations of the efficacy of lithium for late-life depression, previous studies on younger subjects demonstrated the efficacy and efficiency of *lithium* (Lithobid, Lithate) as an augmentation strategy in the treatment of depression.[37] A report of lithium augmentation specifically in older individuals was first published in 1986 as a small case series of five patients. Subsequently, additional retrospective case series on lithium augmentation of antidepressants, typically a TCA,[38] were reported. A large majority of the cases experienced "complete" or "good" improvement. The largest retrospective case series of lithium augmentation ($N = 51$) was published in 1990,[39] which for the first time gave sufficient consideration to ensuring that an adequate dose of antidepressant had indeed been inefficacious.

While the retrospective reports were robustly positive, prospective trials conducted from the 1990s onward did not find the same large effect sizes. Using rating scales, two small prospective studies ($N = 15$ and $N = 21$) of lithium augmentation reported rates of "complete response" of 20% and 24%, respectively.[6] Lithium augmentation of geriatric TRD has been investigated in five nonrandomized trials; the overall response rate was 42%.[8]

The first *randomized controlled trial* (RCT) comparing lithium augmentation with a switch to phenelzine after antidepressant monotherapy was conducted in 2007.[40] Patients ($N = 29$) who were unable to achieve remission after at least 4 weeks of treatment with a TCA or extended-release venlafaxine were randomly assigned to a 6-week treatment with lithium (target level 0.6–1.2 mEq/L) or were switched to phenelzine (up to 60 mg/d) after a wash-out period. The remission rates were low with both strategies; however, despite the small sample size, lithium augmentation (avg level = 0.71 mEq/L),

with a remission rate of 5/15 (33%) in contrast to 0/14 (0%) for phenelzine, was found to be statistically superior.

Augmentation with Second-Generation Antipsychotics

Several studies with mixed-age samples have reported the benefits of antidepressants combined with *second-generation antipsychotics* (SGAs).[41] A meta-analysis of these studies found that among adults, augmentation with SGAs was more effective than placebo in the treatment of MDD.[42] Four SGAs have been approved by the *U.S. Food and Drug Administration* (FDA) for the treatment of major depression that does not respond to antidepressants: *olanzapine* (Zyprexa) (in combination with *fluoxetine* [Prozac, Sarafem]), *quetiapine* (Seroquel), *aripiprazole* (Abilify, Aristada), and *brexpiprazole* (Rexulti). Of the SGAs, aripiprazole is the most commonly used in treatment of depression in the geriatric population and has the best research evidence in support of its use. One of the initial studies of SGA in late-life depression[43] was a prospective open-label pilot trial (N = 20) of aripiprazole augmentation following 6 weeks of SSRI monotherapy. The subjects were non-remitters. **Fifty percent (50%) of the individuals met the criteria for remission after 6 weeks of aripiprazole augmentation.** Similar results were reported for another open-label pilot study, published in 2009, on aripiprazole augmentation in late-life depression. Sheffrin et al. selected partial responders or non-responders (N = 24) for trials of *escitalopram* (Lexapro) followed by 12 weeks of either duloxetine or venlafaxine. After receiving aripiprazole augmentation for 12 weeks, 50% (12/24) of the participants were in remission, a robust improvement considering that 29.1% of the participants had partial response status at the time of initiation. It must be noted that these patients, unlike those in the previously mentioned studies of shorter duration, were given 28 weeks of antidepressant therapy. Determining whether the improvement resulted from the longer antidepressant therapy or the combination and sequence of medication is difficult; however, the sequence of the use of SSRIs followed by SNRIs makes it easier to attribute the improvement to augmentation therapy. The 12 participants were followed for a median of 27.6 weeks, and none experienced relapse during 6 months of pharmacotherapy.

More recently, the efficacy of aripiprazole in treatment of late-life depression was demonstrated conclusively in a large multi-center randomized, double-blind, placebo-controlled trial.[44] Treatment resistance was confirmed with an open-label trial of venlafaxine. A total of 181 subjects not responding to venlafaxine were randomly assigned to a treatment group receiving aripiprazole augmentation (2–15 mg/day, median final dose 7 mg/day) for 12 weeks or a placebo group. The primary endpoint was remission, assessed via the *Montgomery-Åsberg Depression Rating Scale* (MADRS; score of 10 or less on two final consecutive visits). A higher percentage of subjects experienced remission with aripiprazole augmentation compared to those on placebo: 44% vs. 29% (p = 0.03) with a number needed to treat (NNT) of 6.6. Of the subjects treated with aripiprazole, Akathisia and Parkinsonism were experienced by 26% and 17%, respectively.[44]

Support for use of *risperidone* (Risperdal) in treatment of late-life TRD is based on the results of an open-label treatment phase of a larger study by Alexopoulos et al.[45] The study reported on the open-label addition of 0.25–1 mg/day of risperidone to 20–40 mg/day of *citalopram* (Celexa). The patients in the study had had at least one nonresponse to an antidepressant trial of citalopram. Ninety-three (93) subjects entered the open-label treatment phase with risperidone augmentation. Of the 89 patients who completed risperidone augmentation, 67.7% (63/93) achieved symptom remission.

Switch to Other Antidepressants

SNRIs (Duloxetine and Venlafaxine)

In an RCT of geriatric TRD, paroxetine (10–60 mg/day; mean, 26 mg/day) was compared to venlafaxine (75–300 mg/day; mean, 165 mg/day).[46] The treatment response was monitored via the *Clinical Global Impressions* scale, HDRS, and the *Geriatric Depression Scale*. The study reported statistically significant changes in both groups in all three outcome measures. The mean HDRS showed greater improvement with venlafaxine than with paroxetine treatment (–19.5 compared to –12.5). Both medications were well tolerated, and none of the participants dropped out because of medication side effects.[46]

The effectiveness of *duloxetine* (Cymbalta, Irenka; 60–120 mg/day; median, 90mg/day) in the treatment of geriatric TRD was observed in an open-label study. The

dosage used in the trial was higher than the typical 60 mg/day dose used in clinical practice. Fifty percent (50%) of the subjects met the full criteria for response, and 17.5% met the criteria for partial response. The median response time was 12 weeks. A total of five participants (12.5 %) discontinued medication because of side effects.[47]

Monamine Oxidazse Inhibitors (MAOIs; Selegiline)

Sunderland et al.[48] studied the effects of high doses of *selegiline* (Emsam, Zelapar; 60 mg/day) in 16 participants in a placebo-controlled cross-over study. HDRS scores showed significant improvement, 37.4%, after 3 weeks of selegiline treatment, thus suggesting that high-dose selegiline can be an effective treatment of geriatric TRD. The high-dose selegiline was well tolerated without significant clinical side effects.

Sequential Treatment Protocols

Kok et al.[49] reported the outcomes of 3 years of sequential treatment protocols in geriatric TRD. Eighty-one (81) patients were recruited from a 12-week RCT comparing venlafaxine and nortriptyline. Patients who did not achieve remission were offered various sequential treatment options, including lithium augmentation, switch to TCA, switch to phenelzine, switch to SSRI, or ECT. Of the patients, 96.3% achieved response, and 84% achieved remission within 3 years of treatment. Thus, augmentation with lithium resulted in a high remission rate (63.6%) in treatment-resistant geriatric patients.

Thyroid Hormone Supplementation

Although not often used, thyroid hormone augmentation (particularly with *triiodothyronine* [T3]) is an appropriate augmentation treatment strategy that has been endorsed in multiple depression guidelines, including those of the American Psychiatric Association.[50] The beneficial effects of T3 augmentation of TCAs for TRD have been demonstrated in multiple RCTs.[51] In the *Sequenced Treatment Alternatives to Relieve Depression Study* (STAR*D) study, which included geriatric subjects, T3 augmentation (up to 50 mg/day) resulted in a 24.7% remission rate, compared to a 15.9% remission rate with lithium augmentation, in treatment resistant patients who had failed at least two antidepressant medication trials. Although the remission rates were not statistically different, T3 was better tolerated than lithium in this trial.[52]

Methylphenidate

The efficacy of *methylphenidate* (Concerta, Daytrana) augmentation in late-life MDD has been demonstrated in open-label studies.[53, 54] In a 16-week double-blind RCT for geriatric depression among 143 subjects with MDD, methylphenidate (5–40 mg/day), in combination with citalopram (20–60 mg/day), led to greater and faster improvement compared to citalopram and placebo or methylphenidate and placebo.[55] Despite promising results for late-life MDD, little research has focused on the use of methylphenidate as a potential augmenting agent in late-life TRD.

Ketamine

In recent years, ketamine, an *N-methyl-D-aspartate* (NMDA)-receptor antagonist, has emerged as a treatment option for TRD. The rapid efficacy of ketamine infusion in TRD has been demonstrated in multiple RCTs, with a single infusion showing results lasting up to 7 days. In a meta-analysis of ketamine trials, the response rates with ketamine treatment at 24 h, 72 h, and day 7 were 52.2%, 47.9%, and 39.8%, respectively.[56] The beneficial effects of intravenous ketamine use in geriatric patients with TRD have been shown in seven case reports.[57] While ketamine has not been studied in RCTs for geriatric TRD, the safety and efficacy of subcutaneously administered ketamine have been investigated in one double-blind RCT.[58] While the preliminary results are encouraging, ketamine use in geriatric subjects requires further study, particularly with regard to establishing safety and tolerability.

Omega-3 Fatty Acids

Eicosapentaenoic acid and docosahexaenoic acid, *omega-3 fatty acids* (OFAs), have been studied as treatment for MDD in adults. Despite early promise, the results are mixed. One meta-analysis reported significant clinical efficacy for major depression,[59] but two other meta-analyses reported a lack of efficacy. In addition, the clinical trials were considered to be generally of low quality and subject to publication bias.[60, 61] OFAs have also been studied as treatment for late-life depression. A meta-analysis of four studies reported a large effect for OFA supplementation,

as compared with placebo, in geriatric patients with mild to moderate depression.[62] OFAs have not been studied for late-life TRD specifically; thus, further research is needed before clinical use in this patient population can be recommended.

Table 2:
Major Pharmacological Treatment Strategies of Late-Life TRD Studied Specifically in Clinical Trials for Late-Life TRD

Switch to SNRIs:
- Venlafaxine
- Duloxetine

Switch to MAOIs:
- Selegiline
- Phenelzine

Lithium Augmentation:
- SSRI + Lithium
- SNRI + Lithium
- TCA + Lithium

Atypical Antipsychotics:
- Aripiprazole augmentation

Maintenance Pharmacological Treatment Following Adequate Response in Late-Life TRD

At present, there is insufficient evidence to determine the advantages and risks of continued augmentation treatment in late-life TRD patients who have received adequate symptom benefits from an acute trial of augmentation treatment.[6] However, there is some indirect evidence to suggest that continued augmentation treatment may potentially be helpful.

In 1996, Reynolds et al. reported a relapse rate of 52.0% (13/25) after the discontinuation of an augmentation agent during the continuation phase.[63] The subjects exhibited late-life TRD and had previously responded to acute-phase augmentation treatment. In the non-augmentation group, the relapse rate was substantially lower (6.1%, 6/99), indicating that geriatric TRD subjects responding to acute-phase augmentation strategies may require the continuation of augmentation agents to maintain the response. In a naturalistic prospective study, published in 2001, of combined antidepressant plus lithium treatment, 52.4% (11/21) of the subjects relapsed after the discontinuation of lithium. The patients who relapsed had been on lithium significantly longer than those who did not relapse (2.5 years vs 1.4 years of treatment).[64]

The open-label risperidone augmentation treatment by Alexopoulos et al. cited above was followed by a 24-week double-blind maintenance phase during which the remitted subjects received citalopram which was augmented with either risperidone or placebo. A similar number of subjects from both groups relapsed (risperidone: 56%, placebo: 65%). The risperidone group showed a greater median time to relapse (105 days vs 57 days); however, this difference did not reach statistical significance ($p = 0.069$).[45]

Non-pharmacological Interventions:

Psychotherapy

Psychotherapy is an effective but frequently underutilized treatment option for geriatric depressed patients.[65] A meta-analysis of 27 trials ($N > 2000$ patients) that compared different psychotherapies with different controls found significant clinically moderate to large effects in favor of psychotherapy.[66] The CoBalT trial helped to demonstrate that *cognitive behavioral therapy* (CBT) is an effective adjunct to the usual care for primary care patients with TRD.[67] Interpersonal psychotherapy has demonstrated greater efficacy than CBT; however, there is less evidence specific to older adults with TRD.[68] Although the research on the effectiveness of psychotherapy in late-life TRD is limited, it is clinically prudent to use psychotherapy as a treatment strategy in TRD to maximize the chances of response, particularly if the patients were not previously treated with psychotherapy.

ECT

With remission rates as high as 75%, ECT is considered the most effective treatment modality for MDD.[69] This is substantially higher than the remission rates of approximately 25–35% with antidepressants. For TRD, the response rates with ECT are typically 50% and higher.[69] This is also the case for geriatric subjects. A review of the literature suggests that the acute response in geriatric subjects is similar to, or even better than, that in younger patients. However, the time course of response

to ECT may possibly be longer for geriatric subjects, thus indicating that ECT should not be discontinued in the absence of a rapid response.[69] Despite the evidence for its efficacy, ECT remains underused in the geriatric population.

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) has been approved by the FDA for the treatment of TRD in adults. In a review of the literature on rTMS for geriatric depression, Sabesan et al.[70] reported five uncontrolled trials with mixed-aged populations (mean age >60) and two uncontrolled trials with geriatric subjects. The response rates in the uncontrolled trials ranged from 18% to 58.5%. Two of these studies reported a diminishing treatment effect with increasing age, but two other studies did not find such an association. Sabesan et al. also found four randomized controlled trials that included geriatric subjects with a mean sample age of >60. Two of the trials reported no benefit compared to sham treatment, and two reported a significant benefit. Among the trials reviewed by Sabesan et al., one conducted by Jorge et al.[71] demonstrated the efficacy of rTMS in geriatric subjects with vascular depression. Sebasan et al.[70] concluded that the results of the reviewed trials did not negate the utility of rTMS in treating geriatric patients with depression.

Summary and Conclusions

TRD in late life is common but poorly studied. TRD is typically defined as an inadequate response to at least two antidepressant trials of adequate dose and duration; however, the definitions used in clinical research studies vary. The many diagnostic variables involved in late-life TRD require detailed consideration and assessment and include incipient dementia, comorbid medical conditions, psychotic features, treatment tolerance and adherence, treatment duration, and antidepressant selection. Pharmacological strategies for treatment of late-life TRD include switching to SNRIs or MAOIs or augmenting treatment with lithium, second-generation antipsychotics, or thyroid hormones. Lithium and aripiprazole currently have the best, though still limited, evidence-based support. The efficacy of intravenously administered ketamine has been demonstrated in multiple trials in adults with TRD, and it holds promise as an intervention for geriatric TRD. However, further research is required to determine the efficacy and tolerability of ketamine in this patient population. Non-pharmacological strategies, including psychotherapy, for treating late-life TRD remain understudied, but ECT is widely considered as the most effective strategy. There is insufficient evidence to recommend continued pharmacological augmentation treatment in geriatric subjects with TRD following remission achieved by acute treatment; however, indirect evidence suggests that continued augmentation treatment could potentially be efficacious, at least in some cases.

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Multiple-Choice Questions

53. The management of treatment-resistant depression in the elderly is particularly difficult because of:

A. Multiple comorbid illnesses.

B. Interactions with medications for other disorders.

C. Incipient dementia.

D. All of the above

54. Why is paroxetine *not* considered a suitable option for the treatment of geriatric patients?

A. Higher anticholinergic effects

B. Long half-life

C. Decreased efficacy

D. Lack of research evidence

55. Of the agents listed below, which has the best evidence of efficacy as an augmentation agent in the treatment of late-life treatment-resistant depression?

A. Haloperidol

B. Carbamazepine

C. Lithium

D. Valproic acid

56. Which of the following is considered to be the most clinically effective intervention among the treatment modalities available for late-life treatment-resistant depression?

A. ECT

B. SSRIs

C. CBT

D. Antipsychotics

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Best Practices in CME

Management of Treatment-Resistant Depression in Late Life

By Burhan Khan; Anam Zehra, MBBS; Asim Shah, MD; Awais Aftab, MD

ID#: L003417

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

The information provided in this article will be useful for psychiatrists, particularly geriatric psychiatrists, who will be treating cases of ***treatment-resistant depression*** (TRD) in the geriatric population. TRD in late-life is common and poorly-studied; however, it requires special considerations. This paper outlines the clinical assessment and management of TRD in geriatric subjects. It discusses the appropriate assessment of the diagnostic variables related to treatment resistance and evaluates the available treatment options for TRD in late life on the basis of the research evidence. TRD is typically defined as an inadequate response to at least two antidepressant trials of adequate dose and duration; however, the varying definitions have been used in clinical research studies.

Key Point 1: Assessment of Late-Life TRD

Several diagnostic variables are involved in late-life TRD, and they require detailed consideration and assessment. The diagnostic variables to be considered in the assessment of late-life TRD include incipient dementia, comorbid medical conditions, psychotic features, treatment tolerance and adherence, treatment duration, and antidepressant selection.

Key Point 2: Pharmacological Strategies

The pharmacological strategies for late-life TRD include switching to SNRIs and selegiline and augmenting treatment with lithium, second-generation antipsychotics, and thyroid hormones. Lithium and aripiprazole augmentation currently have the best evidence-based support; however, the body of research for late-life TRD is limited. Ketamine may emerge in the future as a treatment option for this patient population.

Key Point 3: Non-Pharmacological Strategies

Non-pharmacological strategies, including psychotherapy, for late-life TRD remain very understudied; however, ECT is widely considered in practice to be the most effective strategy for late-life TRD.

Key Point 4: Continued Augmentation Treatment

There is insufficient evidence to recommend continued augmentation treatment in late-life subjects with TRD following the remission of depression achieved through acute treatment; however, the indirect evidence suggests that continued augmentation treatment could potentially be efficacious, at least in some cases.

Notes

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Care of Pregnant Woman with Severe Mental Illness

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

KEYWORDS: Severe mental illness • Pregnancy • Depression • Psychosis • Bipolar disorder

LEARNING OBJECTIVES: This lesson will enable clinicians to (1) understand the importance of a multidisciplinary approach to the care of women with severe mental illness during the perinatal period; (2) define and describe treatment strategies for the various types of psychiatric disorders seen in pregnant women; (3) review pharmacologic considerations for women with severe mental illness during pregnancy and lactation; and (4) discuss the ethical considerations in the care of this unique population.

LESSON ABSTRACT: Caring for a woman with severe psychiatric illness during the perinatal period can pose clinical challenges; therefore, understanding the symptoms and the available treatment options and resources can lead to better clinical decisions and outcomes for the woman and the newborn. In the case of severe mental illness in a pregnant patient, a multidisciplinary effort is necessary for achieving the optimal coordination of care.

This lesson aims to define and to describe treatment strategies for the various types of psychiatric disorders seen in pregnant women, to review the pharmacologic considerations for women with severe mental illness during pregnancy and lactation, and to discuss the important ethical principles to be considered in the care of this unique population.

In general, patients with severe mental illness should be referred to or co-managed with a psychiatrist. For a patient who exhibits decision-making abilities, a discussion to explain the risks and benefits of pharmacologic treatment options and psychotherapy, if indicated and available, is warranted.

COMPETENCY AREAS: This lesson addresses clinicians' patient care by providing a framework for understanding the effective treatments for severe mental illness in pregnant patients. It also addresses clinicians working in interdisciplinary teams by facilitating mutual understanding and cooperation, as well as the integration of care to ensure safe and comprehensive treatment for pregnant patients with severe psychiatric disorders.

Introduction

Caring for a woman with severe psychiatric illness during pregnancy can pose clinical challenges; therefore, understanding the symptoms and the available treatment options and resources can lead to better clinical decisions and outcomes for the woman and the newborn.

Uncomplicated mental illnesses can often be treated in the primary care setting.[1] However, for optimal care, patients with a known psychiatric disorder should be referred to or co-managed with a psychiatrist, preferably prior to conception.[2,3,4] Untreated psychiatric illness in pregnancy causes not only maternal suffering; it is also associated with poor adherence to prenatal care, as well as inadequate diet, substance misuse, postpartum depression, impaired bonding between mother and infant, an increased risk of self-harm, and, in rare cases, infanticide.[2,5,6] Pregnant women are also less likely than non-pregnant women to use mental health services.[7] Therefore, interdisciplinary interventions and the involvement of psychiatrists when appropriate are critical for this population.

Because *major depressive disorder* (MDD), *bipolar disorder* (BD) and psychosis from schizophrenia, or schizoaffective disorder are associated with poor outcomes that have implications for maternal and fetal wellbeing, this lesson addresses the treatment of these conditions during pregnancy specifically. Upon the completion of this lesson, clinicians will understand the importance of a multidisciplinary approach to the care of women with *severe mental illness* (SMI) during the perinatal period. In addition, they will be able to define treatment strategies for various types of psychiatric disorders, to review the pharmacologic options available during pregnancy and lactation, and to elaborate on the ethical considerations in the care of this population.

Epidemiology and History

The decision to involve psychiatry in the care of pregnant patients with mental illness depends on the severity of the illness. In general, the presence of suicidal or homicidal ideations, manic or psychotic symptoms, impairment in daily functioning, and agitation or behavior that puts self or others in danger are considered red flags and clear indications for requesting a psychiatric consultation.

Depression in Pregnancy:

It is estimated that depression will affect 13 to 23% of women during the period from conception to birth and 11 to 32% of women during the first three months following childbirth.[4,8] **Deaths from maternal suicide exceed deaths from pregnancy-related hemorrhage and hypertensive illnesses.**[5] Few studies have examined suicidality in the peripartum and postpartum periods, but the data suggest that while pregnant women have lower suicide rates than women in the general population, when suicide is successful, the weapons used are more lethal.[9]

The strongest risk factor for MDD during pregnancy is a previous history of depression. Other risk factors include a family history of depression or BD, adverse experiences in childhood, single motherhood, having more than three children, low income, age younger than 20, domestic violence, cigarette smoking, and insufficient social support.[10] Postpartum depression is more common in women with prenatal depression, and it may lead to difficulties with infant care, mother-infant attachment, care of other children, and the relationship with the woman's partner.[4,10,11]

Bipolar Disorder in Pregnancy:

BD affects 0.5 to 1.5% of individuals in the United States. It has an onset typically around late adolescence or early adulthood, thus placing women at risk throughout their reproductive years. One-quarter to one-third of women with BD will decompensate during pregnancy or the postpartum period and suffer from either a depressive, mixed, or manic episode. The postpartum period is also a time of high risk for both the first onset or the exacerbation of symptoms related to this condition. Most important, when untreated, BD can increase the likelihood of impulsive and risky behaviors, substance misuse, poor adherence to prenatal care, and suicide.[12] Despite the many risks associated with pregnancy in this population, this disorder is not a contraindication for pregnancy.[13]

The clinical factors that may be associated with the relapse of previously well-controlled BD during pregnancy include a brief period of clinical stability prior to conception, the discontinuation of pharmacotherapy between six months prior to conception and three months after conception, unplanned pregnancy, existing psychiatric

comorbidity, the duration of the illness for five or more years, or a history of at least one recurrent mood episode per year following the onset of BD.[14]

Approximately 40 to 56% of pregnant women with BD experience perinatal mood episodes, though pharmacotherapy may reduce the occurrence.[15] The risk of recurrence is greatest during the first trimester. A study indicated that 67% of patients experienced a mood episode during the first trimester, 23% during the second, and 10% during the third. The most common morbidity in this population is depression. Another study found episodes of major depression in 42% of patients, mixed episodes in 32%, and mania or hypomania in 26%.[14]

Psychosis in Pregnancy:

New-onset psychosis during pregnancy is rare. Though estimates vary, one study found that the risk of developing an SMI in pregnancy was estimated at 7.1 per 10,000 per year.[16] Psychosis can be present in several psychiatric disorders, including MDD, severe with psychotic features; bipolar I disorder, manic or depressed with psychotic features; schizophrenia; schizoaffective disorder; or brief psychotic disorder.[17] The risk factors for acute psychosis in pregnancy include a previous history of this condition, preexisting psychotic or mood disorders, and a family history of psychosis.[18]

Postpartum psychosis is relatively rare, with a prevalence of 0.1 to 0.2%; however, women are more likely to experience psychosis during the period following childbirth than at any other time in their lives. Several studies have shown the *relative risk* (RR) of hospital admission for psychosis to be higher during the first month postpartum (RR 1.09 to 21.7) than at any other time in a woman's life.[19, 20, 21] Approximately half of these episodes were the first psychotic episode, while the others had had prior hospitalizations for psychosis. The risk factors for postpartum psychosis include personal and family histories of psychosis in pregnancy, BD, first pregnancy, or the recent discontinuation of mood stabilizers. Postpartum psychosis is highly associated with BD. An analysis of more than 54,000 births over a 12-year period found that 120 women had had psychiatric hospitalizations for psychotic disorders during the first 90 days postpartum.[19] Among these 120 mothers with postpartum psychosis, approximately 75% were diagnosed with bipolar or schizoaffective disorder, and 12% had schizophrenia.

Assessment and Diagnosis

Depression in Pregnancy:

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)[17] defines major depression as the presence of five or more of the following symptoms during the same two-week period, with the symptoms representing a change from previous functioning and with at least one of the first two symptoms being:

- **Depressed mood most of the day, nearly every day;**
- **Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day;**
- **Significant weight loss when not dieting or significant weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day;**
- **Insomnia or hypersomnia nearly every day;**
- **Psychomotor agitation or retardation nearly every day;**
- **Fatigue or loss of energy nearly every day;**
- **Feelings of worthlessness or excessive or inappropriate guilt nearly every day;**
- **Diminish ability to think or concentrate, or indecisiveness, nearly every day;**
- **Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt, or a specific plan for committing suicide.**

The symptoms cause clinically significant distress or impairment in functioning, but they are not the result of the direct physiological effects of a substance, a medical condition, or bereavement.[17] Severe MDD may include suicidal or homicidal ideation or related behavior, aggression, psychotic features and poor judgment.[22] The National Institute for Health and Clinical Excellence recommends that all women who are pregnant or are considering pregnancy be asked about their personal and family histories of psychiatric disorders and treatment,

in addition to being asked the routine questions about antenatal depression (see Table 1).[11] The *American College of Obstetricians and Gynecologists* (ACOG) recommends that all women be screened for depression at least once during the perinatal period with a standardized and validated tool.[23] The U.S. Preventative Services Task Force recommends the *Edinburgh Postnatal Depression Scale,* which has been validated for use during pregnancy, and the *Patient Health Questionnaire 9* (PHQ-9) as useful screening tools.[24] If a woman screens positive for depression, then multidisciplinary care involving a psychiatrist is recommended.

Table 1:
Screening Questions for Depression During Pregnancy

- During the past month, have you been bothered by feeling down, depressed, or hopeless?
- During the past month, have you been bothered by having little interest or pleasure in doing things?
- If the answer to either question is "yes," ask: "Is this something you feel you need or want help with?"

Bipolar Disorder in Pregnancy:

Bipolar I disorder is characterized by manic episodes, which are distinct periods of abnormally and persistently elevated, expansive, or irritable moods and abnormally and persistently increased activity or energy lasting at least one week and present most of the day, nearly every day (or any other duration if hospitalization is necessary). During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

- **Inflated self-esteem or grandiosity;**
- **Decreased need for sleep (e.g., feeling rested after only three hours of sleep);**
- **Being more talkative than usual or feeling pressure to keep talking;**
- **Flight of ideas or subjective experience that thoughts are racing;**
- **Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed;**
- **Increase in goal-directed activity (either social, work- or school-related, or sexual) or psychomotor agitation (i.e., purposeless non-goal-directed activity);**
- **Excessive involvement in activities that have a high potential for painful consequences (e.g., unrestrained buying sprees, sexual indiscretions, or foolish business investments).**

This mood disturbance is sufficiently severe to cause marked impairment in functioning or to necessitate hospitalization. The episode is also not attributable to the physiological effects of a substance or another medical condition.[17]

Bipolar II disorder is characterized by at least one hypomanic episode and one major depressive episode. In contrast to a manic episode, a hypomanic episode lasts at least four consecutive days and is not severe enough to cause marked impairment in functioning or to necessitate hospitalization.[17]

Psychosis in Pregnancy:

Psychosis is classically defined as a disturbance of an individual's perception of reality. Psychosis can present with a variety of symptoms, including delusions, hallucinations, and thought disorganization.[17] Delirium and medical causes must be investigated when a woman presents with psychosis. With psychotic episodes of a primary psychiatric disorder, the common symptoms include paranoia, auditory hallucinations, and disorganized thoughts or behavior. When the symptoms include disorientation, fluctuations in the level of consciousness, visual or tactile hallucinations, or other neurological issues, the suspicion of a medical etiology increases.[18] Many recreational substances can also present with psychotic symptoms; thus, an evaluation of recent substance use should be included.

Treatment Strategies

Medication Management in Pregnancy and Lactation—Addressing a Stigma:

Most psychiatric disorders require pharmacologic treatment, but in this population, the stigma and fear surrounding the use of medications are high. Physicians, including psychiatrists, are often hesitant to prescribe psychotropic medications to lactating mothers because of these concerns and others surrounding medico-legal liability. The evidence suggests that un-medicated psychiatric illnesses have significant detrimental effects on mothers and the infants.[25] For example, a depressed mood during pregnancy is reported to be associated with poor attendance at antenatal clinics, substance misuse, low birth weight, and preterm delivery.[26] Overall, depressed mothers provide less responsive caregiving; they are more likely to discontinue breastfeeding early or to have problems breastfeeding; and they are less likely to comply with recommended safety practices, such as the use of car seats. In addition, their children have lower rates of preventive healthcare use and vaccinations.[27]

According to the Centers for Disease Control and Prevention, more than 90% of pregnant women take at least one medication, and more than two-thirds take at least one prescription drug. A study found that between 2008 and 2013, approximately 15% of reproductive age women (ages 15–44) in the U.S. with private health insurance had filled a prescription for an antidepressant.[28] **Most antidepressants, with the exception of *paroxetine* (Paxil, Brisdelle), are safe during pregnancy.** In December 2005, a public health advisory issued by the *U.S. Food and Drug Administration* (FDA) highlighted the concern that the use of paroxetine during the first trimester might present a higher risk for cardiac defects than the use of other *selective serotonin reuptake inhibitors* (SSRIs).[29] *Lithium* (Lithobid, Lithate) has been associated with Epstein's anomaly (malformation of the tricuspid valve and right ventricle).[30] Valproate has a black box warning about "[fetal risk, particularly neural tube defects, other major malformations, and decreased IQ.]"[31] *Carbamaze-pine* (Tegretol, Carbatrol) has been linked to similar side effects; however, the ratio is as much as four times less than that for valproate. Some studies have found benzodiazepines to be associated with an increased risk for oral cleft palate; however, other studies have not found this association.[32] The recommendations for the treatment of acute mania and hypomania have been based on trials that excluded pregnant women.[33] The medications to be avoided during pregnancy can be found in Table 2.

Table 2:
Medications to Avoid in Pregnancy

- Paroxetine
- Lithium*
- Valproate
- Carbamazepine
- Benzodiazepines

* Unless recommended by the consultant psychiatrist

Most psychiatric disorders during the postpartum period require the same standard treatments as those provided during the non-postpartum period except that consideration must be given to the safety of these medications during lactation.[34] The general pharmacological principles regarding lactation can be found in Table 3. **All psychotropic medications are secreted in breast milk, but a majority are present only in low concentrations and can be used safely in lactating mothers.** Breastfeeding should not be discouraged unless a complicating factor, such as psychosis, suicidality, or infanticide risk, is present. The specific considerations for selecting psychotropic medications can be found in Table 4.

Treating Depression during Pregnancy:

Pregnant women are often hesitant to engage in treatment because of their concerns for the baby's well-being; thus, it is important to emphasize the effects of maternal depression on an unborn child. Untreated depression during pregnancy has been associated with increased risks of miscarriage, low birth weight, impaired fetal growth, and preterm birth.[35] The infants of depressed mothers, compared to those of mothers who are not depressed, have been found to have increased irritability, fewer facial expressions, and higher cortisol levels. In addition, they are at risk for developmental delays and behavioral problems in later childhood.[36, 37]

For women with pre-existing depression who are planning pregnancy or are already pregnant, the severity of

Table 3:
General Principles of Psychotropic Use during Lactation

- The lowest effective dose should be used, and polypharmacy should be avoided where possible.
- When practical, breastfeeding can be timed to avoid peak drug levels in the milk; alternatively, the milk can be expressed for subsequent feeding.
- The benefits of breastfeeding for the mother-infant dyad versus the risks of harm to the infant from medication exposure should be judged on a case-by-case basis. The infant is at risk of exposure to the side effects of the medication and the effects of the mother's untreated psychiatric illness. The clinical decision-making should take both types of exposure into account.
- All infants of lactating mothers receiving psychotropic medications should be monitored for any general or specific adverse effects. Most psychotropic medications can cause sedation.
- Breastfeeding should be stopped if any adverse effects secondary to medication use are suspected.
- Extra caution should be exercised with infants who are premature or have renal, hepatic, cardiac, or neurological impairments because they are at a greater risk for side effects even from low levels of medication exposure.
- In general, the treatment of psychiatric illness in the mother, especially when the risk of relapse is high, takes precedence over the benefits of lactation. It may be preferable to cease breastfeeding rather than to cease the use of medication if the two are determined to be incompatible.
- If the mother has taken psychiatric medication during pregnancy up to the time of delivery, her continuation of the medication during lactation will minimize withdrawal or discontinuation symptoms in the infant.
- The effects of any medication on the mother's ability to care for her baby should be taken into consideration.
- Psychiatric medications for which there are more published safety data should be preferred over recently marketed medications with less available data unless otherwise clinically indicated.
- Where possible, medications with short half-lives, high protein binding, low oral bioavailability, and high molecular weight should be preferred.
- Psychotropic medications with long pediatric half-lives should be used very cautiously, given the risk of build-up in an infant's plasma over time.
- The maternal caregiver role should be acknowledged, and the mother's preferences regarding lactation should be respected without judgment.
- Psychological interventions should be offered to all patients who choose not to continue using psychotropic medications during lactation.
- The measurement of the serum levels of the psychotropic medications in the infant is not routinely recommended.

Table used with permission.[34]

past and current episodes, their response to treatment, and their preferences should guide the treatment decisions.[2] Mild to moderate depression can generally be treated at the outpatient level of care but with close monitoring for a possible progression to severe depression. Many pregnant patients with mild to moderate depression can be treated initially with psychotherapy, such as interpersonal psychotherapy or *cognitive behavioral therapy* (CBT).[38] Antidepressants are used typically for patients who have responded to medications for prior episodes. They are also prescribed for severe MDD.[6] Pregnant women with severe MDD often require hospitalization for stabilization and safety.[39] SSRIs are considered the first line of treatment in the peripartum and postpartum periods.[40, 41] **The evidence suggests that *sertraline* (Zoloft), as well as *citalopram* (Celexa) and *escitalopram* (Lexapro), has a good response rate and little to no risk of teratogenicity. These are therefore reasonable medications to prescribe initially for women who have not previously been on antidepressants.**[42]

Treating Bipolar Disorder in Pregnancy:

Because of the high risk of recurrent mood episodes, particularly in patients who have discontinued pharmacotherapy, preconception and prenatal maintenance treatments are often indicated for female patients with BD who plan to or do become pregnant.[14] Despite the differences in severity and presentation, the treatment of mania and hypomania are similar. **Although the use of atypical antipsychotics during pregnancy has increased dramatically in recent years, first-generation antipsychotics are typically used in the treatment of severe mania or hypomania in a pregnant patient, most commonly, *haloperidol* because there is more data regarding its use during pregnancy.**[2, 33, 43] Its availability in oral and intramuscular formulations (the intravenous route is avoided because of the higher

Table 4:
Psychotropic Medications and Lactation

Antidepressants	• ***Fluoxetine*** (Prozac, Sarafem) has a longer half-life and is more likely to accumulate. • ***Doxepin*** (Silenor, Zonalon) has been linked to sedation and respiratory depression in infants. Its use during lactation is contraindicated. • ***Monoamine oxidase inhibitors*** (MAOIs) should be avoided, given the significant drug interactions, dietary restrictions, and lack of safety literature. • ***Bupropion*** (Zyban, Aplenzin) can lower the seizure threshold.
Mood Stabilizers	• Lithium is present in high amounts in milk, and it has the potential for toxicity. It should be administered with caution during lactation, with regular clinical and laboratory monitoring of the infant. • ***Lamotrigine*** (Lamictal) has the potential to cause a life-threatening rash. Monitoring and immediate discontinuation with appearance of any rash is recommended.
Antipsychotics	• A limited amount of data is available on antipsychotics in general; however, there are no significant safety concerns. The exception is ***clozapine*** (Clozaril, FazaClo), which can potentially lead to agranulocytosis.
Benzodiazepines	• Benzodiazepines can accumulate in neonates because of immature hepatic (cytochrome P450) enzymes. • There is a risk for ***central nervous system*** (CNS) and respiratory depression. Clinical monitoring is required. • Benzodiazepines, such as ***diazepam*** (Valium, Diastat), with long half-lives should be avoided.

Table used with permission.[34]

risk of QT prolongation and Torsades de Pointes) also makes it a more convenient choice. Oral disintegrating tablets of *risperidone* (Risperdal) or *olanzapine* (Zyprexa) are other alternatives, but only olanzapine, *ziprasidone* (Geodon, Zeldox), and *aripiprazole* (Abilify) are available as short-acting injectables.[44, 45, 46, 47] The injectable forms are reserved for patients for whom other options have failed. Other first-generation antipsychotics, particularly *chlorpromazine* (Largactil, Thorazine), can also be used in patients unable to tolerate the minimal dose of haloperidol.[48] An alternative to switching antipsychotics in patients who develop dystonia or parkinsonism is the addition of *diphenhydramine* (Benadryl, Banophen), which has been shown to have low teratogenicity, to the existing regimen.[49]

For pregnant patients with moderate to severe manic episodes who do not respond to sequential trials of medications, *electroconvulsive therapy* (ECT) is an efficacious and safe option for both the mother and the fetus. ECT is often viewed as having fewer side effects and posing fewer risks than untreated BD or teratogenic medications.[6, 50, 51] Psychosocial interventions focus primarily on increasing adherence to treatment, improving functioning, minimizing sleep deprivation, and preventing relapse.[52] Structured daily activities, which minimize sleep deprivation and reduce mood lability, are extremely important during pregnancy.

Treating Psychosis in Pregnancy:

Psychosis in pregnancy has been associated with an elevated risk of preterm delivery and the birth of

small-for-gestational-age infants, as well as stillbirth and infant death. In addition, it can affect a woman's ability to care for herself and her child.[25, 53] When treatment options are being discussed with women with known psychotic disorders, the risks of continuing antipsychotic treatment need to be balanced against the risks of untreated illness. It is important to note that the current guidelines and clinical practices for the use of antipsychotics in women with non-affective disorders during pregnancy and the postpartum period are not based on evidence from randomized controlled trials.[54] To date, no association has been consistently found with antipsychotic use and adverse maternal or fetal outcomes.[55] Therefore, psychosis during pregnancy can be treated with first- or second-generation antipsychotics at the lowest effective dose. Mothers with postpartum psychosis should be hospitalized, given the high risk of infant neglect, infanticide, and suicide.

Clinical Case:

A 27-year-old woman, G1P0*, at 17 weeks' gestation, presented to the psychiatrist as a referral from her obstetrician for positive depression screening. For the previous two months, she had "felt more tired than usual" and had had difficulty falling asleep because of worry about being a mother. She also reported that it was hard for her to make herself do anything and that she often felt guilty about the situation. The patient also endorsed the symptom of a decreased appetite but denied having difficulty concentrating. She denied having suicidal or homicidal ideations, auditory or visual hallucinations, or manic or hypomanic symptoms. While in college, she saw a psychologist for depression but did not take an antidepressant. She had no medical problems. She took prenatal vitamins, had no allergies, and denied a family history of psychiatric illnesses. She also denied alcohol, tobacco, or illegal drug use.

After a discussion of the known risks and benefits of antidepressants versus untreated depression in pregnancy, the patient agreed to a trial of sertraline and CBT. With coordinated psychiatric and obstetric care, the remainder of the patient's antepartum course was uneventful. She responded well to a combination of pharmacotherapy and psychotherapy and delivered a healthy baby. The patient continued sertraline postpartum after discussing the benefits and risks of continuing to use the same antidepressant while breastfeeding.

Legal and Ethical Issues

Pregnancy and SMI add more layers of complexity to the already complex task of dealing with treatment needs, legal rights, and ethical responsibilities regarding not one but two patients: the mother and the fetus or newborn.[56, 57] Understanding the general legal and ethical standards that apply to medical care and having a clear plan for systematically addressing these issues can help caregivers to make rapid and correct treatment decisions. While in most medical settings it is the physician who bears the final medico-legal responsibility for treatment decisions, the ideal is a collaborative process that includes nursing, obstetric, and psychiatric providers. An ethics committee and risk management should be among the considerations as well.

The major intersection between legal statutes and ethical standards with regard to medical care revolves around the issue of informed consent for treatment, including both detention in the hospital and the use of specific procedures.[58, 59] With regard to mental illness, the legal and ethical principles are very clear and simple: Every person has capacity until otherwise demonstrated. A psychiatric diagnosis in and of itself does not constitute incapacitation unless the symptoms affect the patient's ability to make rational decisions. While applying for mental health commitment to initiate obstetrical care might seem helpful in cases of "clear" mental illness, it may complicate treatment in most states. Mental health commitment applies to psychiatric detention only, thus making the involuntary use of psychotropic medications (except for immediate danger) illegal in many cases.

Beneficence to the unborn child as an ethical justification for treatment is a gray area. In medical care, the burden is on the caregiver to prove and to document incapacitation that is based on the patient's decision-making process. There are a number of useful tools, such as the open-source aid to capacity evaluation, which is available at www.utoronto.ca.jcb_ace, and the outline presented by Magid and colleagues, for facilitating capacity

* *Pregnant for the first time and not yet delivered.*

determination.[60, 61] The medical team must explain the recommended treatment, including the risks, benefits, and available alternatives. The capacity assessment therefore consists of the "5 W's":

1. **Will you explain the treatment we just recommended?**
2. **What is your understanding of how this treatment can help you?**
3. **What is your understanding of what could happen if you don't have the treatment?**
4. **What alternatives could you choose instead?**
5. **Why have you decided to accept or to refuse?**

There is a degree of fluidity in capacity standards, a "sliding scale" that takes into account the relative risks or benefits of the recommended treatment, the risks of refusal, and the knowledge of the patient's prevailing values and beliefs.[62] Babbitt et al., building on previous work by Coverdale, McCullough, and Chervenak, designed an algorithm for responsible decision-making with regard to capacity and treatment (see Figure 1).[63, 64, 65, 66]

The treatment paradigm is based on ongoing assessments of capacity: treatment "as usual" (i.e., by informed consent) when capacity is present and efforts to restore decision-making capacity when it is absent. The use of antipsychotics to assist in both behavior management and the restoration of the ability to participate in treatment decisions is well established for cases in which the primary cause of incapacitation relates to psychiatric symptoms, regardless of the etiology.[67, 68, 69] The risk-benefit profiles for both the mother and the newborn favor administering appropriate amounts of these medications to the mother.

When a patient lacks capacity, caregivers must seek a surrogate decision-maker (usually an advanced directive, a medical power of attorney, family members, or a hospital-designated alternative) and act to restore the patient's capacity. It is the legal and ethical responsibility of the surrogate to make decisions that are based on the values and beliefs of the patient (if known) or that are in the best interest of the patient in the absence of knowledge of the patient's wishes.[70, 71] Even if a surrogate decision-maker can be found, care providers are ethically and legally bound to continue efforts to restore the patient's capacity. At any time that the delivery becomes imminent or the mother's or the fetus' medical condition becomes emergent, the treatment team generally has a legal and ethical mandate to proceed with "normal treatment" that is within the standard of care for the community.

Intrapartum, Postpartum, and Neonatal Considerations

Obstetricians are skilled in the management of normal labor and delivery and the associated complications; however, their expertise might be challenged when a pregnant woman presents to the *labor and delivery* unit (L&D) with SMI, agitation, or psychosis.

One aspect of a complete intake in the obstetric *emergency room* (ER) or the L&D should be a psychiatric history that includes, but is not limited to, current working diagnoses, outpatient care, previous hospitalizations, current medications, and comorbid conditions, such as substance use disorder. Previously administered outpatient screening questions can be asked again to compare the current and past clinical statuses or the severity of the symptoms.

Collaborative multidisciplinary care by obstetric, psychiatric, pediatric and anesthesia teams, as well as the nursing staff, social workers, and child protective services promotes the best outcomes for the mother and the newborn and the safety of the obstetric staff. Interdisciplinary planning is necessary for being prepared to provide care for women with mental illness who may arrive at the prenatal setting and for managing the ongoing team conferences for existing patients who will arrive for labor.

A safety assessment is a key component of any psychiatric evaluation, but the clinical dilemma becomes more complex when the analysis includes the patient and the fetus or newborn. It is also important to review the hospital's protocol for managing severe agitation, such as de-escalation through verbal redirection followed by the offer of oral medication for calming the patient, with injectables as the next strategy if the previous measures have not been effective.[72] The use of soft restraints is usually considered the last resort. The addition of qualified psychiatric staff to provide continuous supervision is very helpful, particularly in cases where the patient is considered to be in imminent danger of doing harm to herself or others.

Figure 1:
Algorithm for Responsible Decision Making and Clinical Care

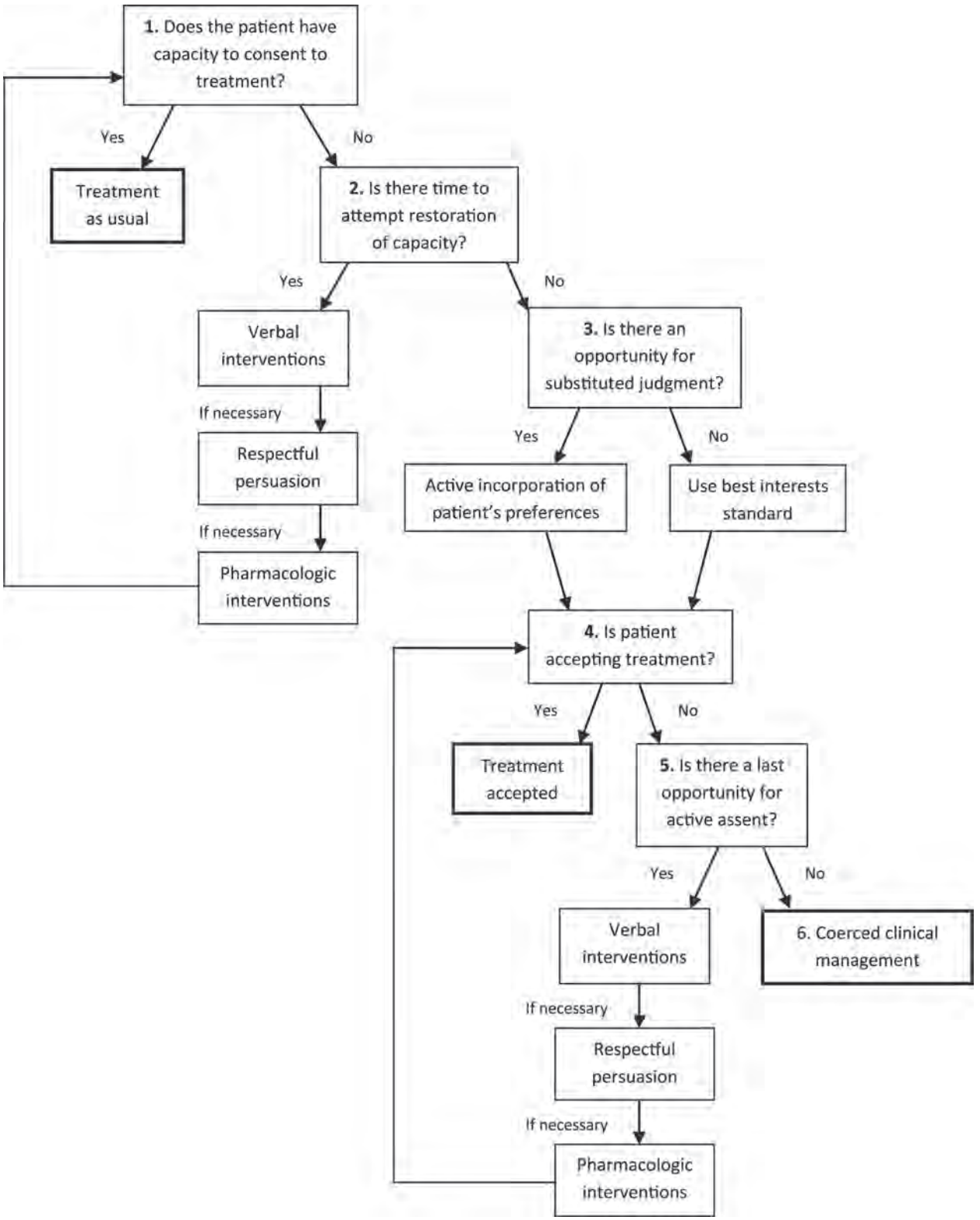

Table used with permission.[63]

Regulating psychotic behavior and managing severe agitation often require the administration of medications. A mother with suicidal and homicidal ideations or psychotic or manic symptoms will not be capable of caring for herself and her newborn, so immediate consultation with a psychiatrist is indicated in order to start the appropriate medication and to facilitate admission to a psychiatric facility for further management. The guidelines from several countries recommend that mothers be admitted with the baby whenever possible, but such settings are not easy to find.[73]

Women who are compliant and stable on their existing psychotropic medications should continue with the same regimen during and after labor. The presence of a psychiatric diagnosis does not automatically mean that the patient's care will be complicated. However, as was noted above, it is also very common for pregnant patients to discontinue all psychotropic medications as soon as they find out that they are pregnant. Such non-adherence to treatment increases the risk of recurrence or the exacerbation of psychiatric symptoms.[14, 74]

Summary

Caring for women with severe psychiatric disorders before, during, and after pregnancy can be a challenge for all providers. The paucity of randomized controlled trials and evidence regarding the use of psychotropic medications in pregnant women presents additional challenges in the care of this population. The appropriate training of clinicians in the recognition, management, team coordination, and relevant ethical issues is critical to providing optimal care and improving clinical outcomes.

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L003418

Multiple-Choice Questions

57. Which of the following characteristics of a medication make it preferable for use during lactation?

A. Short half-life.

B. Low protein binding.

C. High oral bioavailability.

D. Low molecular weight.

58. A 33-year-old G4P2012* at 39 weeks' gestation with gestational diabetes and a history of bipolar I disorder is admitted to the L&D unit for the induction of labor. At 3:00 am, the on-call provider receives a call that the patient has become progressively irritable and is attempting to pull out her IV In addition, she is shouting that she has to go home to email the president her idea for ending world hunger. Her speech is pressured. The provider's attempts to redirect the patient result in increasing agitation, and the patient has declined to take any oral medication. What is the best next step in management?

A. Administer IV lorazepam.

B. Administer IM haloperidol.

C. Administer IM diazepam.

D. Order the use of two-point soft restraints.

59. A 38-year-old G3P2001* presents to the ER painfully contracting at 40 weeks' gestation. She initiated prenatal care at 20 weeks' gestation because she did not realize that she was pregnant. The patient is admitted to the L&D unit for expectant management of her labor. A review of the medical record shows that she has schizophrenia and has been taking risperidone at a dose of 2 mg twice a day. She denies having any active delusions, audiovisual hallucinations, or suicidal or homicidal ideations. What is the most appropriate course of action?

A. Discontinue her antipsychotic medication.

B. Consult psychiatry and evaluate the patient's decision-making capacity.

C. Change the medication to haloperidol.

D. Notify child protective services.

** G=total pregnancies, P= #full term delivery, # preterm delivery, # abortions, # living children*

60. Which of the following antidepressants should be avoided in pregnancy?

A. Sertraline

B. Escitalopram

C. Citalopram

D. Paroxetine

Best Practices in CME

Care of Pregnant Woman with Severe Mental Illness

Jin Y. Han, MD; Sherrill Sorensen, DNP, MHL, RN, CENP; Melissa Wilkes Requenez, MD; Elizabeth David, MD; Natalie Pon, MD; Ksenia Voronina, MD; C. Haley Walker; Asim Shah, MD

ID#: L003418

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Clinicians are often challenged in caring for women experiencing severe psychiatric illness during pregnancy. This course aims to underscore the importance of a multidisciplinary approach to the care of women with severe mental illness during the peripartum and postpartum periods, to define and to describe treatment strategies for various types of psychiatric disorders in pregnant and lactating women, and to discuss the possible ethical and intrapartum issues.

Key Point 1: Depression in Pregnancy

All women should be screened for depression at some point during the peripartum or postpartum period with a validated assessment tool, such as the *Edinburgh Postnatal Depression Scale* or the *PHQ-9*.[23, 24] Few evidence-based guidelines are available for the treatment of depression, specifically during pregnancy. More randomized controlled trials are needed to evaluate the effects of such treatment on the embryo or fetus during pregnancy or the offspring during lactation.[40] Based on the results of studies on depression in the general population, SSRIs are considered first-line treatment.[41, 42] Sertraline at the lowest effective dose is therefore recommended for treatment-naïve patients. Pregnant patients with existing depression should maintain their treatment regimens with appropriate psychiatric follow-up visits. The exception is women taking paroxetine due to its risk of cardiac defects during the first trimester so an alternative SSRI should be considered.[29]

Key Point 2: Bipolar Disorder in Pregnancy

The diagnosis of bipolar disorder is made through the identification of manic or hypomanic episodes as defined by the *DSM*.[17] The data on antipsychotics are limited, but there are no significant safety concerns. The exception is clozapine, which can potentially lead to agranulocytosis.[34] First-generation antipsychotics at the lowest effective dose are typically used as first-line therapy in the treatment of severe mania or hypomania in pregnant patients. Based on the available safety data, most psychiatrists will use haloperidol.[33, 43]

Key Point 3: Psychosis in Pregnancy

Psychosis is defined by poor reality testing and the presence of hallucinations, delusions, and/or disorganization.[17] The potentially reversible causes of psychosis, such as substance use, delirium, or other medical causes, must be investigated in a pregnant or postpartum patient who presents with psychosis. Most of the available safety data are for the first-generation antipsychotics; however, neither the first-generation nor

the second-generation antipsychotics have been consistently associated with birth defects or other adverse outcomes.[55] Postpartum psychosis requires inpatient management for stabilization because of the risks to the mother and the newborn.

Key Point 4: Ethics of Caring for Severe Mental Illness in Pregnant Patients

A psychiatric diagnosis in and of itself, even in the presence of significant psychiatric symptoms, does not constitute incapacitation unless those symptoms affect the patient's ability to make reasonable and rational decisions. An ongoing assessment of decision-making capacity, with consideration of beneficence towards the mother and the fetus or newborn, is important for preserving the patient's autonomy.[60, 61] In the absence of decision-making capacity, efforts should be made to restore decision-making capacity. These should include the identification of the underlying cause of the loss of capacity and, when indicated, the use of psychotropic medications.

Key Point 5: Intrapartum Care for Patients with Severe Mental Illness

A psychiatric history that includes working diagnoses, outpatient care, previous hospitalizations, current medications, and comorbid conditions should be obtained during the initial evaluation in the L&D unit or the obstetrical ER. A safety assessment should be performed in the L&D unit on patients with suspected or known severe mental disorders. Ideally, it should be a multidisciplinary effort involving psychiatrists. Hospitals often have their own protocols for agitation, and these should be reviewed. Generally, de-escalation through verbal redirection should be attempted first, followed by the offer of oral medication to calm the patient, with the use of injectable medication as the next strategy if the previous measures have not proved effective.[72]

L003419

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Navigating Through Psychiatric Disorders Due to Another Medical Condition, Part I: An Overview

Vladimir Bokarius, MD, PhD, QME

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

KEY WORDS: Psychiatric symptoms • Mental illness • Medical conditions • Differential diagnosis

LEARNING OBJECTIVES: On completing this lesson, the clinician will be able to (1) delineate psychiatric symptoms associated with disorders in specific body systems; (2) identify warning signs that a medical condition may underlie the presenting psychiatric symptoms; and (3) incorporate appropriate components of both somatic and psychiatric treatment into the care of patients exhibiting symptoms of psychiatric disorders.

LESSON ABSTRACT: Psychiatric symptomatology is often caused directly by pathological changes in the functioning of body systems other than central nervous system. Research indicates that such potential causes of psychiatric symptoms are often overlooked by providers. As a result, the cause of some psychiatric symptoms is often misdiagnosed or not correctly identified. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), psychiatric disorders caused organically by medical illness are termed disorders due to another medical condition. The purpose of this lesson is to remind providers that mental and behavioral symptoms can be caused by organic medical conditions and may form a basis for elucidating the scope of such diagnoses.

COMPETENCY AREAS: This lesson aims to provide clinicians with knowledge of mental and behavioral symptoms that can be caused by medical conditions. Being informed of underlying organic medical conditions that present as psychiatric symptoms enables clinicians to make differential diagnoses by utilizing informatics and medical knowledge to provide optimal patient care.

Preface

For years, I have been teaching a broad array of healthcare professionals—medical students, residents, and practicing psychologists, as well as nurse practitioners and physician assistants—how to improve their ability to make a differential diagnosis. One of my approaches has been to challenge any clichés with which they may have been indoctrinated. Indeed, my first question is usually as follows:

> *"Say a 32-year-old female presents to your office complaining of impaired sleep, poor concentration, [and] low energy level and is crying throughout the interview—what is her diagnosis?"*

The unequivocal response has been: "depression!" Indeed, these symptoms represent a depressive disorder, but they may also reflect generalized anxiety disorder, a psychotic disorder, or a neurocognitive disorder, or an almost innumerable host of nonpsychiatric medical conditions.

It is important to keep in mind that symptoms of mental illness are not always products of disorders of the mind or brain alone but may be a result of the pathological malfunctioning of any of multiple organs and tissues in the body. In other words, mind and body are one. To evaluate them separately is to support a dualistic fallacy that does not help the sophisticated provider arrive at an accurate diagnosis.

Mental health professionals who have not received any medical training are at the greatest risk of overlooking organic medical conditions that may contribute to the development of psychiatric disorders, because they are usually taught to think of psychopathology solely in terms of psychological phenomena—that is, to overlook potential biological causes of psychological symptoms.

"Psychiatric disorders due to another medical condition" (formerly referred to as "psychiatric disorders due to a general medical condition") comprise a category of psychiatric disorders that are the direct physiologic consequences of specific medical conditions. These disorders must be distinguished from adjustment disorders, the symptoms of which are associated with the patient's attempt to cope with the stress of having a general medical condition or the disability that results from a general medical condition (e.g., anxiety, depression, or aberrant behavior). When faced with patients with an adjustment disorder, providers tend to attribute the presenting symptoms to "another medical condition." This reflects a misreading of the definition of the diagnosis as it appears in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*,[1] wherein disorders due to another medical condition are reserved for individuals with organic conditions who present, usually unbeknownst to them, with psychological symptoms that are caused directly by an organic condition. Patients with such disorders are likely to have prominent physical symptoms of a physical illness of which they are not yet aware or they do not find distressing.

The same applies to the diagnosis of a somatic symptom disorder or illness anxiety disorder. Patients with a somatic symptom disorder exhibit a strong or even obsessive focus on their somatic symptoms and are distressed by the potential significance of their symptoms or their effects on their health, whether such concerns are valid or not. Patients with an illness such as anxiety disorder are often overly concerned about having or acquiring a grave illness. This obsessiveness is not, in fact, physiologically caused directly by any underlying medical condition. As such, neither of these disorders should be considered "due to another medical condition."

Axis III—along which medical conditions relevant to the diagnosis or treatment of a psychiatric condition were listed—was eliminated from the *DSM* in *DSM-5*. Nevertheless, *DSM-5* prompts clinicians to continue to list the medical conditions they need to understand in

DEFINITION: PSYCHIATRIC DISORDERS DUE TO ANOTHER MEDICAL CONDITION [1]

According to DSM-5, to diagnose a psychiatric disorder due to another medical condition, there must be evidence from the history, physical examination, or laboratory/imaging findings that the change in mental health is the direct physiological consequence of another medical condition. The psychiatric diagnosis is not given if the disturbance is better explained by another mental disorder. And, as with all psychiatric diagnoses, the disturbance must also cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

order to manage each patient's mental disorder, whether that disorder is directly responsible for the patient's distress or suspected of being a causative factor in the patient's psychiatric condition. Such a list has no bearing on the diagnosis of a disorder due to another medical condition but should be provided for every patient, regardless of the psychiatric diagnosis. Of note, medical conditions that are irrelevant to the understanding or management of a mental disorder should not be mentioned—a complete list of medical illnesses is appropriate in the medical history, but not in the diagnosis section of the report.

When the principal diagnosis or reason for the patient's visit is a mental disorder due to another medical condition (e.g., a major neurocognitive disorder due to Alzheimer's disease or a psychotic disorder due to a malignant lung neoplasm), the causative medical condition must be listed first, according to the codes of the *International Classification of Diseases* (ICD). It is followed by the principal diagnosis, i.e., the mental disorder resulting from the medical condition.[1] Furthermore, the medical illness should be identified by name within the diagnosis of the mental disorder due to the medical condition.

Background

There is a dearth of epidemiological studies of mental disorders due to another medical condition. One of the best reviews of the literature covers 21 studies in which approximately half (50.1%) of the patients had symptoms of a psychiatric disorder, 58.2% of which had not been diagnosed previously. More than 25% of the physical illnesses in these patients "produced symptoms showing [a] direct relation to the psychopathology of the patient." The authors noted further that "no psychiatric symptoms exist that at times cannot be caused or aggravated by a variety of medical illnesses," pointing out that often when such symptoms arise, patients are erroneously dispatched to psychiatric clinics or private psychiatrists and the latent organic pathology responsible for the symptoms may remain undiagnosed for years or until more pathognomic organic symptoms arise.[2] Many conditions that are not immediately apparent—most being infectious, autoimmune, endocrine, metabolic, or neoplastic in origin—have been shown to have neuropsychiatric manifestations.[3] In a study of 175 patients under psychiatric care, investigators found that 16% had medical conditions that could cause or exacerbate their psychiatric symptoms. These included metabolic abnormalities, neurological disorders, and the adverse effects of medications. Several had a specific disease, such as cancer.[4] A metabolic screening of subjects with psychosis revealed the presence of treatable metabolic disorders in a significant number of participants.[5] The literature on organic causes of depression includes many endocrine, neurologic, infectious, and malignant disorders, as well as vitamin deficiencies among ITS potential causative factors, in addition to iatrogenic depression caused by the side effects of medications.[6]

In an early (1968) study of 250 patients hospitalized with psychiatric disorders, investigators found that the psychiatric problem had been caused by a physical illness in 12% of cases and that 80% of the causative illnesses had been missed by their physicians before admission.[7] In another study, investigators found that in 46 of 100 patients hospitalized with psychiatric disorders who had been screened for physical illnesses before admission, the psychiatric illness had been caused or exacerbated by a medical illness that had been overlooked.[8] In another study by the same author, medical disorders were found to be responsible for psychiatric symptoms in 9.1% of 658 patients seen in psychiatric outpatient facilities. In a review of the medical workup for these patients, the author discovered that 46% had organic medical illnesses that had, until then, not been known to the patient or the patient's physician, which provides further evidence that the patients had not received a careful medical evaluation during the course of psychiatric treatment.[9] In an evaluation of more than 500 patients served by community mental health programs in California, 14% were found to have psychiatric symptoms that had been caused or exacerbated by a medical illness. Interestingly, the program staff had been aware of fewer than half of the significant physical diseases affecting these patients prior to the study.[10] A provider guide to assessing such conditions concludes that "conservative estimates suggest that 10% of persons initially seen in outpatient settings for psychological symptoms have an organic disease causing the symptoms." This figure may be significantly higher among the elderly and in inpatient settings, as well as among patients with symptoms of certain psychiatric disorders.[11]

A review of the death records of more than 2000 outpatients treated for psychiatric disorders revealed the presence of physical illness in more than 80% of them, regardless of the cause of death. Of these, "…one-third were [sic] inadequately diagnosed by their referring physicians."[12] In another study by the same author, in more than 2000 patients treated in psychiatric clinics, 43% of the patients were found to have one or more concurrent physical illnesses. The physical illness had not been diagnosed by the referring source in 46% of these patients: non-psychiatrist physicians had missed one third of them, and psychiatrists missing half.[13] Among U.S. adults with documented medical conditions, it has been estimated that 29% also have a mental illness, whereas 68% of patients diagnosed with a psychiatric condition have comorbid medical conditions.[14] The need to rule out an organic cause of psychiatric symptoms is clearly critical, given the high rate of comorbidity of mental illness and organic conditions.

Other Medical Conditions

More than 100 medical disorders can masquerade as psychological conditions. These disorders may be responsible for psychiatric symptoms in as many as 25% of patients diagnosed with a psychiatric disorder and may contribute to symptoms in more than 75% of these patients.[15]

There is a scarcity of established diagnostic algorithms for mental disorders due to medical conditions. Nevertheless, several authors have made prodigious inroads into this field. I would especially like to praise Barbara Schildkrout, MD, for her multiple publications on this topic and highly recommend her book—*Masquerading Symptoms: Uncovering Physical Illnesses That Present as Psychological Problems*—to those who wish to increase their awareness of this issue and deepen their understanding of the many organic conditions that may underlie mental illness.[15]

Table 1 contains a list of medical conditions sorted by body system and the possible psychiatric manifestations of each. This is not a comprehensive list; it is provided to illustrate the variety of possible causes of symptoms of mental illness rather than to serve as a guide for diagnoses.

Table 1:
Medical Conditions and Psychiatric Presentations

Body System/Condition	Possible Psychiatric Symptoms
Cardiovascular	
Myocardial infarction, arrhythmias, congestive heart failure, mitral valve prolapse	Anxiety, insomnia
Endocrine	
Acromegaly	Depression, irritability, apathy, loss of libido
Addison's disease	Depressed mood, loss of motivation, fatigue, diminished appetite, weight loss, Addisonian crisis-associated psychosis
Cushing's syndrome	Depression, irritability, anxiety, insomnia, mania, and/or psychosis, cognitive deficits
Hyperparathyroidism (including hypercalcemia)	Depression, fatigue, trouble concentrating, irritability (psychosis, confusion, and delirium at higher calcium levels)
Hyperthyroidism	Anxiety, hyperactivity, irritability, difficulty concentrating, depression
Hypoglycemia	Anxiety or panic, irritability, shakiness, emotional lability, confusion, and disorientation; may resemble intoxication
Hypoparathyroidism (hypocalcemia)	Cognitive impairment, anxiety
Hypothyroidism	Women > men. Gradual onset of depression, slowed mental processes
Gastrointestinal	
Hepatic encephalopathy	Toxic delirium with cognitive impairment, lethargy, apathy, subtle personality changes; signs of liver disease are common—a solely neuropsychiatric presentation is rare
Pancreatic cancer	Depression, panic, and anxiety may precede any other psychiatric or physical symptoms
Infectious diseases	
Creutzfeldt-Jakob disease	Anxiety and depression, insomnia and fatigue, irritability, mental slowness, impaired concentration and memory, hallucinations and delusions
Lyme disease	Fatigue, depression, irritability, lability, insomnia, poor concentration, memory impairment
Syphilis	Depression, anxiety, mania, psychosis, personality changes, insomnia, apathy, withdrawal, disinhibition, paranoia, delusions of grandeur, psychosis, delirium, dementia
Autoimmune disorders	
Hashimoto's encephalopathy	Acute psychosis, worsening depression, and declining cognition progressing to altered levels of consciousness with neurological disturbances
HIV/AIDS	Depression; more rarely, mania or psychosis; neurocognitive deficits: mental retardation, impaired executive functioning and attention, learning difficulty
Limbic encephalitis	Drastic psychological decompensation with disturbances in cognition, memory, sleep, mood, depression, anxiety, and agitation, followed by psychosis; rapid onset and development
Systemic lupus erythematosus	Fluctuating symptoms of mood, anxiety, insomnia, tearfulness, subtle cognitive dysfunction, and delirium/psychosis
Kidney disorders	
Uremia (chronic kidney disease)	Irritability, insomnia, depressive symptoms (e.g., fatigue, weight loss, loss of libido), delirium, dementia
Metabolic disorders	
Acute intermittent porphyria	Psychosis, bizarre behavior, anxiety, agitation, depression, catatonia, hypomania, delirium
Niemann-Pick disease	Symptoms of catatonia, visual hallucinations
Wilson's disease	Early onset of irritability, depression, personality changes
Homocystinuria	Psychiatric complications found in 51% of adult patients and include behavioral disorders (physical violence, drug or alcohol abuse), personality disorders (hyperactivity, excessive spending, disinhibition), depression, and obsessive-compulsive disorder

Neurologic diseases associated with movement disorders	
Huntington's disease	Disturbances in executive function and memory; irritability; apathy; and mood disturbances, including impulsive or aggressive behavior
Parkinson's disease	Sleep difficulties, depression with dysphoria, anxiety, apathy, irritability, agitation, hallucinations; cognitive and executive functioning impairments
Neurologic diseases: headaches	
Migraine	Mood instability, irritability, anxiety, difficulty concentration, visual/auditory hallucinations, appetite change, elation or depression and apathy, altered sense of reality.
Neurologic disease: traumatic brain injuries	Amnesia; cognitive deficits depending on which area of brain affected; dementia; executive function; impaired judgment and insight; language difficulties; personality change
Post-concussion syndrome	Amnesia, attention/concentration difficulty, slowed mental processing, anxiety, emotional lability, fatigue
Neurologic Disease: Other	
Brain tumors	Great variety of symptoms, including any type of hallucination, personality changes, mood disorders, anxiety, psychosis, cognitive disturbances, and/or delirium
Multiple sclerosis	Depressive/dysphoric symptoms; emotional lability; anxiety; personality changes; cognitive dysfunction, including dysfunction of executive functioning, memory, and attention/concentration
Myasthenia gravis	Fluctuating symptoms—including fatigue, muscle weakness—that are affected by emotional states and thus often mistaken for illness—anxiety disorder, conversion disorder, or depression
Partial seizures	May masquerade as anxiety, panic attacks, dissociative episodes, impulse control disorders, ADHD, tics, conversion disorder, or psychosis. Effect depends on site of discharge
Normal-pressure hydrocephalus	Apathy, anxiety, psychomotor retardation, memory disturbance
Progressive supranuclear palsy	Impaired cognition; apathy; anxiety; depression; personality changes, including disinhibition
Poisoning/Toxicity	
Arsenic poisoning	In chronic, low-dose poisoning: mood disorder, personality change, or insidious onset of dementia; in high doses: delirium
Carbon monoxide poisoning	In initial or chronic low-dose toxicity: waxing and waning mood disturbances, cognitive deficits. In high doses, virtually all known neuropsychiatric symptoms may be present and may appear after weeks of pseudo-recovery
Lead poisoning	Depending on exposure level, symptoms are "psychological masquerade": insomnia, decreased libido, fatigue, lethargy, confusion
Manganese toxicity	Insidious onset of insomnia, fatigue, apathy, psychomotor retardation, anxiety, irritability, mood lability, personality changes or, alternatively, acute agitated psychosis
Mercury poisoning	Anxiety, pathological shyness, easy blushing, social avoidance, memory and attention deficits
Thallium poisoning	Either (1) acute delirium, agitation, hallucinations, delusions or (2) dementia, intellectual impairment, personality changes
Sleep disorders	
Restless leg syndrome	Early and/or middle insomnia, excessive daytime drowsiness, irritability, difficulty concentrating, secondary depression due to distress about sleep
Sleep apnea	Daytime somnolence, significant decline in daytime functioning as a result of impaired sleep, dysphoria, irritability, variety of cognitive problems, confusion upon waking, social withdrawal
Vitamin deficiencies	
Pellagra	Fluctuating fatigue and malaise, irritability, insomnia, anxiety, depression, psychomotor retardation, memory deficits
Thiamine deficiency (including Wernicke's encephalopathy, Korsakoff's syndrome)	Wernicke's syndrome: acute global confusion, drowsiness, apathy, indifference. Korsakoff's syndrome: severe memory disturbance—anterograde amnesia and retrograde amnesia that may go back several decades, poor insight, confabulation, abstraction difficulty, lack of spontaneity and initiative, disorientation for time and place
Vitamin B12 deficiency	Depression, fatigue, irritability, dementia, delirium

Psychiatric Symptoms Caused by Medical Illness

This section may serve as a "cheat sheet" to facilitate recognition of medical conditions that may cause psychiatric symptoms. Tables 2 through 5 reflect four broad psychiatric categories: anxiety, depression, mania, and psychosis. Note that each of these categories covers a spectrum of symptom severities and subtypes, some or all of which may accompany the medical conditions named.

Table 2:
Anxiety Symptoms Due to Another Medical Condition

Etiology	Specific Condition to Rule Out
Autoimmune	Multiple sclerosis
	Myasthenia gravis
Cardiovascular	Myocardial infarction
	Arrhythmias
	Congestive heart failure
	Anemia and hypovolemia
	Mitral valve prolapse
Endocrine	Adrenal disorders
	Glucose dysregulation
	Parathyroid dysfunction
	Thyroid dysfunction
	Gonadal hormone dysfunction
Gastrointestinal	Colitis
	Peptic ulcer disease
	Esophageal dysmotility
Infectious	AIDS
	Pneumonia
	Tuberculosis
	Mononucleosis
Metabolic	Acidosis
	Electrolyte abnormalities
	Wilson's disease
	Porphyria
Neurologic	Brain tumors
	Cerebrovascular accident
	Encephalopathies
	Epilepsy (especially temporal lobe)
	Pain
	Traumatic brain injury
	Huntington's disease
Respiratory	Asthma
	Pneumothorax
	Pulmonary embolism

Table 3:
Depressive Symptoms Due to Another Medical Condition

Etiology	Specific Condition to Rule Out
Autoimmune	Multiple sclerosis
	Systemic lupus erythematosus
Endocrine	Adrenal disorders
	Thyroid disorders
	Parathyroid disorders
	Gonadal hormone dysfunction
Infectious	Limbic encephalitis
	Creutzfeldt-Jacob's disease
	Neurosyphilis
	Lyme disease
Metabolic	Nutritional deficiencies
Neoplastic	Pancreatic cancer
	Other cancer
Nephrologic	Uremia
Neurologic	Cerebrovascular accident
	Epilepsy
	Normal pressure hydrocephalus
	Traumatic brain injury
	Parkinson's disease
	Huntington's disease
	Brain tumors
Sleep Disorders	Obstructive sleep apnea
	Insomnia (e.g. due to pain)

If You Do Not Look For It, You Will Not Find It!

Three heuristics must be applied to determine whether a presenting mental illness has been caused by a medical condition: (1) the suspected medical illness must be present; (2) a temporal association between the development of the medical condition and the mental illness must be made; and (3) a documented physiological mechanism by which the medical illness is known to cause psychiatric symptoms must be established.

There are, as yet, no guidelines for definitively diagnosing mental illness due to medical condition. There are some red flags, however, that suggest the presence of a link between psychiatric symptoms and a medical condition:

- **Presence of chronic physical illness**
- **Sudden change in mood or personality**
- **Lack of a psychiatric history or a history of symptoms resembling the current one(s) in a patient more than 40 years of age**
- **History of head trauma**
- **Exposure to infections or recent travel to areas in which specific infections are endemic**
- **Neurological symptoms (e.g. cranial nerve abnormalities, abnormal movements), rashes, or edema**
- **Lack of effectiveness of psychopharmacological and psychotherapeutic or worsening of the patient's condition**

When should you suspect that a mental illness has an underlying medical cause? *Always*. Once again—if you do not look for it, you will not find it!

In addition to the red flags just described, be on the alert for the following symptoms in patients with a

Table 4:
Manic Symptoms Due to Another Medical Condition

Etiology	Specific Condition to Rule Out
Autoimmune	Systemic lupus erythematosus
Endocrine	Cushing's syndrome
	Thyrotoxicosis
Infectious	Neurosyphilis
	Creutzfeldt-Jacob's disease
Metabolic	Hepatic encephalopathy
Neurologic	Cerebrovascular accident
	Traumatic brain injury
	Epilepsy
	Brain tumors
	Huntington's disease
	Multiple sclerosis

Table 5:
Psychotic Symptoms Due to Another Medical Condition

Etiology	Specific Condition to Rule Out
Autoimmune	Multiple sclerosis
	Systemic lupus erythematosus
Endocrine	Adrenal disorders
	Thyroid dysfunction
	Parathyroid dysfunction
	Pituitary dysfunction
Infectious	Encephalitis
	Neurosyphilis
	Lyme disease
	AIDS
	CNS parasites
	Tuberculosis
Metabolic	Porphyria
	Wilson's disease
Neurologic	Brain tumors
	Cerebrovascular accident
	Epilepsy
	Traumatic brain injury
	Normal pressure hydrocephalus
	Huntington's disease
	Parkinson's disease
	Tuberous sclerosis
Nutrition: Vitamin Intake	Vitamins A, D, B12
Nutrition: Mineral Intake	Magnesium

psychiatric disorder that may suggest the presence of an underlying organic illness:

- **A change in headache pattern**
- **Visual disturbances, blurred vision, partial vision loss**
- **Speech deficits: dysarthrias or aphasias**
- **Abnormal vital signs**
- **Disorientation and/or memory impairment**
- **Fluctuating or impaired level of consciousness**
- **Abnormal body movements**
- **Frequent urination, increased thirst**
- **Significant weight change—gain or loss**

Be thorough, collect a comprehensive history, review available records, and get collateral information. Do not hesitate to request a consultation with specialists in other fields.

Do not assume that a certain symptom "must" be psychological in origin. People with an established mental illness can acquire a medical illness that results in additional psychiatric symptoms at any time.

Practice Points

The importance of making the distinction between psychiatric disorders due to another medical condition in various contexts cannot be underestimated. Clinical contexts include the emergency department or an inpatient setting, outpatient practice, or correctional institution. A correct diagnosis not only facilitates timely, appropriate, and effective treatment, it also allows you to avoid unnecessary treatment and the financial burden associated with it while reducing expenses associated with incorrect triaging and patient disposition.

In a medical-legal context, the presence of a potentially causative medical condition may be relevant not only from a clinical perspective, but also in determining the cause of psychiatric injury, calculating a permanent disability rating, apportioning permanent disability, and assigning liability for treatment.

When managing a patient with psychiatric symptoms due to another medical condition, it is crucial to treat the underlying medical condition. Do not hesitate to order tests or make referrals to confirm your suspicions. An appropriate follow-up should always be established. For example, if you refer a patient for a sleep study, make sure you review the results and refer the patient to a sleep specialist, when appropriate. If you order a metabolic panel, be prepared to review the results and refer the patient for follow up, if needed. The role of psychopharmacology in treatment is usually secondary (e.g. administering *haloperidol* (Haldol) for delirium in addition to the treatment prescribed for the cause of the delirium, or the use of antipsychotics to resolve perceptual disturbances caused by head trauma or psychotic agitation/aggression in patients with Huntington's disorder). Note that comorbid psychiatric disorders should also be treated. The role of psychotherapy in these cases is primarily educational and supportive, with the therapist explaining the diagnosis and the need for adherence to treatment of the underlying medical condition.

About the Faculty

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Multiple-Choice Questions

61. Psychiatric Disorders Due to Another Medical Condition are:

A. Antecedent to and serve as useful red flags for the potential onset of a medical condition.

B. Caused in 3 out of 4 cases by anxiety and distress the patient feels about having a medical condition

C. Invariably are caused by a somatic medical condition

D. Diagnosed by exclusion, i.e. when all possible psychogenic causes have been ruled out.

62. Which of the following diagnoses is an example of a correctly coded "Due to Another Medical Condition" disorder?

A. Adjustment Disorder Due to Myocardial Infarction

B. Somatic Symptom Disorder, With Predominant Pain, Due to Cervical Disc Disease

C. Psychotic Disorder Due to Huntington's Disease

D. Illness Anxiety Disorder Due to Another Medical Condition

63. Disorders of which of the following body systems can give rise to psychiatric disorders?

A. Endocrine

B. Cardiovascular

C. Respiratory

D. All of the above

64. Which of the following scenarios would *not* serve as a red flag when determining whether a psychiatric presentation is caused by a general medical condition?

A. The patient is in his 20s and has no known history of substance abuse but presents with weight loss, excessive exercise, and concern about body image.

B. The patient is in his 20s and is seen subsequent to a motor vehicle accident with loss of consciousness and a subsequent diagnosis of confusion accompanied by dysphoria and poor concentration.

C. The patient is in her 40s and presents with symptoms of depression and anxiety with gradual onset following a recent trip to the Philippines.

D. A patient in his 60s with a known history of schizophrenia presents after 3 nights of sleeplessness, during which he has been nonresponsive to an adjustment in medication.

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Best Practices in CME

Navigating Through Psychiatric Disorders Due to Another Medical Condition: Part 1

By Vladimir Bokarius, MD, PhD, QME

ID#: L003419

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Psychiatric symptomatology is often caused directly by pathological changes in the functioning of body systems other than central nervous system. Research indicates that such potential causes of psychiatric symptoms are often overlooked by providers. As a result, the cause of some psychiatric symptoms is often misdiagnosed or not correctly identified. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), psychiatric disorders caused organically by medical illness are termed disorders due to another medical condition. The purpose of this lesson is to remind providers that mental and behavioral symptoms can be caused by organic medical conditions and may form a basis for elucidating the scope of such diagnoses and change a treatment approach.

Key Point 1: Background

Symptoms of a psychiatric disorder are not necessarily manifestations of mental illness. Don't allow your formal specialty training to preclude the performance of a differential diagnosis. Remember that many medical illnesses can cause psychiatric symptoms

Key Point 2: Evaluation & Differential Diagnosis

When evaluating a patient with psychiatric symptoms, always suspect an underlying medical condition or substance use as the cause of those symptoms until you can rule it out by taking a thorough medical and substance use history. Order any tests that may be necessary when a medical cause of symptoms of a psychiatric condition is suspected.

Key Point 3: Patient Monitoring

Monitor the patient's progress during psychopharmacological and psychotherapeutic treatment and revisit the possibility of a medical cause of psychiatric symptoms if no response is achieved with adequate trials of the selected medications. Make appropriate referrals and establish a proper follow up.

Key Point 4: Psychoeducation

Educate your patients about the organic cause(s) of their disease and the relationship to psychiatric symptoms, as well as treatment options. Reassure the patient that if they experience psychiatric symptoms beyond those caused by the medical condition, you will address them through treatment either in parallel with the medical condition or after the underlying medical condition has been stabilized.

Notes

L003420

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Navigating Through Psychiatric Disorders Due to Another Medical Condition, Part 2: Clinical Case & Analysis

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

KEY WORDS: Psychiatric symptoms • Mental illness • Medical conditions • Differential diagnosis

LEARNING OBJECTIVES: On completing this lesson, the clinician will be able to (1) delineate psychiatric symptoms associated with disorders in specific body systems; (2) identify warning signs that a medical condition may underlie the presenting psychiatric symptoms; and (3) incorporate appropriate components of both somatic and psychiatric treatment into the care of patients exhibiting symptoms of psychiatric disorders.

LESSON ABSTRACT: Psychiatric symptomatology is often caused directly by pathological changes in the functioning of body systems other than central nervous system. Research indicates that such potential causes of psychiatric symptoms are often overlooked by providers. As a result, the cause of some psychiatric symptoms is often misdiagnosed or not correctly identified. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), psychiatric disorders caused organically by medical illness are termed disorders due to another medical condition. The purpose of this lesson is to remind providers that mental and behavioral symptoms can be caused by organic medical conditions and may form a basis for elucidating the scope of such diagnoses.

COMPETENCY AREAS: This lesson aims to provide clinicians with knowledge of mental and behavioral symptoms that can be caused by medical conditions through the analysis and discussion of clinical case studies. Being informed of underlying organic medical conditions that present as psychiatric symptoms enables clinicians to make differential diagnoses by utilizing informatics and medical knowledge to provide optimal patient care.

Introduction

The following vignettes are from the author's own practice and are provided to illustrate clinical aspects of the theories presented in Part I of this lesson, namely, how medical conditions may lead to or interact with psychiatric presentations.

Clinical Case 1

The patient is a 56-year-old African-American woman who was brought by her husband to the emergency department. Her husband reports that for the past 4 days, the patient has been having a "manic episode." He reports that she was brought home yesterday by the police after running out of the house and down the street naked. He is familiar with the patient's diagnosis and presentation and is certain she was experiencing a manic episode. He states that his wife takes her medications regularly.

The patient has a lifelong history of bipolar disorder since a young age and has had multiple episodes of depression and mania, but she had not demonstrated these symptoms over the last 2 years. Furthermore, she never ran outside naked before.

- **The patient has no history of illicit substance use.**
- **Her medical history is significant for chronic back pain, obesity, and hypertension.**
- **She is currently taking lithium 600 mg twice daily and lisinopril 20 mg once daily. She also takes ibuprofen 600 mg for exacerbated back pain.**
- **She has no known drug allergies.**
- **There is no pertinent environmental or developmental history.**

The mental status examination reveals a tall, obese woman dressed in elaborate, brightly colored clothing and wearing excessive makeup, a large and unusual-looking hat, a ring on every finger, and several necklaces and bracelets. She has pressured speech and talks non-stop; it is difficult to redirect the content of her speech. It is also difficult to understand what she is talking about. She boasts that she has four doctoral degrees, which her husband denies. She is euphoric with an expanded, intense affect.

- **Vital signs: within normal limits (WNL).**

We recommended admission to an inpatient unit, and the patient agreed to go. Her initial treatment consisted of *quetiapine* 50 mg twice daily, with the goal of rapid titration to 300 mg twice daily. The following tests were performed: *complete blood count* (CBC), comprehensive metabolic panel, *thyroid-stimulating hormone* (TSH) levels, and urinalysis. The next-day results were all WNL, including lithium (0.9 mmol/L). There was no change in the patient's behavior, the staff reporting that she slept 4 hours at night. Within 3 days, the quetiapine dose had been titrated up to 300 mg twice daily, which she tolerates well. She now sleeps 5.5 hours each night and has shown no other changes in behavior. Considering that she has not demonstrated a response to treatment, and considering her age and the atypical presentation of the manic episode, we decided to carry out *magnetic resonance imaging* (MRI) of her brain. The MRI revealed a 2-cm, space-occupying lesion in her right parietal cortex.[1, 2] The patient was referred to neurosurgery, where the lesion was identified as a meningioma and she was scheduled for surgery. The psychiatric symptoms completely abated after surgery.

Clinical Case 2

The patient is a 26-year-old incarcerated white woman who was brought under custody to the prison hospital because of "weird behavior" that has lasted since she was transferred to this prison several days ago. The patient claims to "speak in tongues," which she demonstrated through rapid, apparently unintelligible speech. The prison staff reported that when they opened the cell port to give her food, she tried to stick her leg out. When asked why she was doing that, she responded, simply: "I want to get out."

The patient admits to a past psychiatric history but cannot explain it. She does not remember her diagnosis, but she recalls trials of various psychotropic medications, including haloperidol, risperidone, and

her current medications: olanzapine 30 mg at bedtime and divalproex sodium ER 250 mg twice daily.

- **She admits to using multiple illicit substances, including crystal meth, crack cocaine, marijuana, and alcohol. She reports that she has been sober since she was incarcerated about a year ago.**
- **She denies any significant medical history and believes that she is healthy.**
- **She has no known drug allergies.**
- **There is no pertinent environmental or developmental history.**

The mental status examination revealed a thin, disheveled woman of average height who is withdrawn and making eye contact only intermittently. Her speech ranges from normal to "speaking in tongues." She exhibits episodic motor agitation with purposeless movements. Her mood is neutral; her affect is constricted and blunted. Her thought processes appear to be disorganized and not goal-directed. She does not demonstrate any overt delusions or paranoid, suicidal, or homicidal ideation. She is alert and oriented to self, time, place, but not to situation (i.e., she does not understand why she has been brought to the hospital). She claims that she does not remember many events in her life and is a poor historian. Her attention and concentration are impaired; she requires frequent repetition of statements and questions before she can provide any answers.

- **Vital signs: WNL. Next-day laboratory study results revealed a valproate level of 24 mcg/mL. The CBC and comprehensive metabolic panel findings were WNL. Her urine toxicology test was negative for known drugs of abuse.**

The patient was diagnosed with psychotic disorder not otherwise specified. Because she was already taking a high dose of *olanzapine* and her valproate level was below the therapeutic range, the valproate dose was doubled to 500 mg twice daily. Two days later, she was still "speaking in tongues," but much less frequently. Additionally, she was episodically able to provide a coherent history, but would suddenly pause, stare, and "speak in tongues" for a minute before returning to normal speech. It became apparent that she was having brief seizure episodes.[3] The olanzapine was tapered off then stopped. The valproate dose was tapered up and stabilized when her blood drug level reached 85 mcg/mL (which is in the high therapeutic range). No neurologist was available to evaluate her, but the available staff felt that she appeared to be stabilized. She no longer "spoke in tongues," was able to maintain a coherent conversation, and no longer demonstrated odd motor activities.

Clinical Case 3

The patient is a 45-year-old man from the Pacific Islands who had been brought under custody to the prison hospital. The patient is known to have a history of anger and aggression tantrums and had been diagnosed with antisocial personality disorder. On presentation, however, he was euphoric—laughing, smiling, and telling everyone he loves them, singing and dancing nonstop. This behavior continued for approximately 8 hours. This is the first known episode of such behavior in this patient.

It was not known if the patient had ever been diagnosed with any major psychiatric disorders, and he is not taking any psychotropic medications. He has a prescription for albuterol prn for asthma and omeprazole for gastroesophageal reflux disease.

- **The patient has a history of abusing multiple substances, even while in prison.**
- **He has no known drug allergies.**
- **There is no known pertinent environmental or developmental history.**

The mental status examination revealed a tall, overweight man with diaphoresis (his T-shirt was soaked through with sweat). He answers questions briefly, but immediately returns to singing a mixture of songs. He is constantly in motion, even when not actively dancing. He is euphoric and emanates good will and love toward all. He is hyper-alert and oriented to self, time, place, and situation.

- **Vital signs: Heart rate (HR) is 115 bpm. Blood pressure (BP) is 140/90 mmHg. Respiratory rate (RR) is 20 bpm.**
- **A urine toxicology screen is negative for drugs of abuse. Because his behavior was disruptive in the hospital environment, he was given an intramuscular injection of 5 mg of haloperidol with lorazepam 1 mg and diphenhydramine 0.5 mg.**

The next morning, the staff reported that the patient had been dancing and singing all night and did not sleep. When seen, he was still in a "great" mood—not dancing or singing, but speaking rapidly. No psychotic symptoms were noted. He was given a prescription for oral haloperidol 5 mg 3 times daily and demonstrated normal mental status and behavior 2 days later.

During a confidential conversation, he admitted using a full inhaler of albuterol (60 doses) within an hour prior to developing symptoms.[4]

Clinical Case 4

The patient is a 45-year-old white woman who was voluntarily admitted to an inpatient psychiatric unit because of a chronically depressed mood and passive suicidal ideation. She reports progressive changes in mood over the last 4 years and her symptoms currently meet the criteria for major depressive disorder. She has not been responding to medications. She reports that her suicidal thoughts are based on a sense of hopelessness and feeling that she would be better off dead. She has not made plans or shown intention to commit suicide but admits thinking about it a lot. She was unable to work during the last year and has been authorized by a psychologist to remain off work. She has been in psychotherapy ever since the symptoms of depression began; she has found the sessions to be helpful for the time she is in the session but not for the time between sessions. For the past 12 months, she has been seeing a psychiatrist, who prescribed *escitalopram* up to 20 mg for 2 months and mirtazapine 45 mg for 3 months; she is currently taking venlafaxine ER 150 mg and bupropion ER *(24h)* 300 mg. She also takes *t*razodone 100 mg and finds that it is somewhat helpful for sleep. All medications were prescribed once daily; trazodone at bedtime.

- **She has no previous psychiatric history.**
- **She has no history of illicit substance use.**
- **She has not had a physical examination in 5 years but states that she never had any medical problems in her life and considers herself healthy. She has not started menopause.**
- **The patient has no physical complaints other than low energy and fatigue. She also reports a decreased appetite, although she has not lost weight in the past 5 years.**
- **She has no known drug allergies.**
- **There is no pertinent environmental or developmental history.**

The mental status examination revealed a middle-aged woman who reports feeling depressed and appears to be depressed—with constricted, blunted affect; mild psychomotor retardation; and soft speech. She has passive suicidal ideation. Her ability to concentrate is reduced and she is forgetful. She has impaired judgment and insight.

- **Vital signs: HR is 52 bpm. BP is 110/60 mmHg. RR is 16 bpm.**
- **She has dry, coarse hair; dry skin; mild periorbital puffiness, and +1 pitting edema.**
- **Based on these findings, laboratory tests were ordered that included the TSH level.**

Her TSH was 8.6 mIU/L, which is consistent with hypothyroidism.[5] She was referred to internal medicine and given a prescription for levothyroxine. She was discharged 3 days later with follow-up in the outpatient psychiatric clinic and outpatient internal medicine clinic. All of her psychotropic medications were gradually discontinued, with the exception of trazodone. Three months later, she was free of psychiatric symptoms. Trazodone was discontinued, and she was advised to discontinue psychotherapy.

Clinical Case 5

The patient is an 82-year-old Latino with mild Alzheimer's disease, well-controlled diabetes, and well-controlled hypertension. He takes metformin 1000 mg twice daily, *lisinopril* 20 mg, hydrochlorothiazide 12.5 mg, donepezil 10 mg, and memantine 10 mg twice daily, as well as a multivitamin pill. He has resided in a skilled nursing facility for the last 3 years. He had an episode of agitation and anger during the first year but has been calm, manageable, and redirectable most of the time—except when it comes to taking a shower, which he continues to resist. The facility staff reports that he has been agitated and responding to internal stimuli (i.e., talking to himself most of the time). He has not been sleeping well at night. Instead, he has been, wandering around the facility and the entering the rooms of other patients, thereby disturbing the therapeutic milieu for the last 3 days. His symptoms have been waxing and waning. The staff asked that he be given medication that could calm him down, because he was no longer manageable and was becoming increasingly aggressive, both verbally and physically.

- **He has no history of illicit substance use.**
- **He is allergic to sulfa.**
- **There is no pertinent environmental or developmental history.**

The mental status examination revealed that the patient is confused and disoriented and demonstrates moderate psychomotor agitation. His thought process is derailed. He responds to internal stimuli; his response is manifested by his communicating with invisible people. He is easily agitated, raising his voice to the level of shouting. He has been observed assuming a fighting stance while passing other patients.

- **Vital signs: HR is 90 bpm. BP could not be measured because of the patient's resistance; it was last measured in the morning at 138/80 mmHg. RR is 18 bpm. Last measured body temperature was 98.9°F.**
- **The patient does not have a cough, and his lungs are clear on auscultation. He is resistant to a full physical examination.**

Based on this presentation and the sudden changes in the patient's behavior, level of consciousness, and cognition, a diagnosis of delirium was made. Stat urinalysis was ordered. Oral haloperidol (the agent of choice for delirium) 0.5 mg three times daily was prescribed.[6] Urinalysis was positive for a urinary tract infection, which is not uncommonly asymptomatic in the elderly.[7] A urine sample was sent for cultures, and empirical treatment was initiated with cephalexin. The patient responded well to treatment, and his symptoms of delirium improved considerably within a week. Haloperidol was tapered off over the following week, by which time the patient's mental status had returned to baseline.

Clinical Case 6

The patient is a thin, 37-year-old Asian woman who presents at an outpatient psychiatric clinic with complaints of anxiety and middle insomnia with multiple awakenings. She reports that these awakenings "feel like waking up from a nightmare; I feel panicked, with my heart beating fast," but she does not remember her dreams. She has headaches in the morning. She further reports a recent diagnosis of hypertension that is poorly controlled. Her morning BP continues to be elevated despite taking propranolol £ up to 140/90 mmHg on some mornings, compared to 130/70 mmHg in the evenings). She also reports having low energy, fatigue, impaired concentration, forgetfulness, and sleepiness during the day with episodes of dozing off. The symptoms started insidiously about a year ago. She was diagnosed by her family physician with generalized anxiety disorder, insomnia, and hypertension. A trial of zolpidem resulted in worsening of daytime sleepiness and did not improve the middle insomnia; it was discontinued. A trial of mirtazapine (current dose: 30 mg) was not effective, either. For this reason, the patient was referred for psychiatric evaluation.

- **The patient has no psychiatric history or history of substance abuse, and no significant medical history. She denies having any psychosocial stressors at the time of symptom onset. She denies a history of snoring.**
- **She has no known drug allergies.**
- **She is positive that her recent laboratory test findings were WNL.**

The mental status examination reveals an apparently anxious and tired woman exhibiting mild psychomotor agitation and slightly constricted affect. She loses the line of the interview episodically and spent more than the average amount of time completing the intake paperwork.

- **Vital signs: HR is 72 bpm. BP is 132/80 mmHg. RR is 14 bpm.**

Because of her complaints of significant daytime sleepiness, an *Epworth Sleepiness Scale* was administered. Her score was 12, which, in conjunction with morning headaches, poorly controlled blood pressure, and other reported symptoms, prompted a suspicion of obstructive sleep apnea, 8, 9, 10 even though the patient is not overweight and denied snoring.[10] The patient was given a pulse oximeter to use at home for 3 consecutive nights. The pattern of oxygen saturation at night confirmed that her nocturnal breathing was impaired and prompted a referral for a sleep study. The diagnosis of obstructive sleep apnea was confirmed. Mirtazapine was tapered off. The patient started using a CPAP (continuous positive airway pressure) machine. In one month, all of her symptoms decreased significantly, and she decided against further follow up with psychiatric services.

Conclusions

These cases illustrate the essentiality of obtaining a medical history and additional workup when indicated even when patients present with psychiatric symptoms only. The above six real cases are good representations of such situations. A few of them illustrate conditions which are common yet can be easily overlooked by both medical and psychiatric providers. Several others depict conditions more rarely seen, and therefore serve as important reminders to stay vigilant of multiple possible etiologies of psychopathology.

About the Faculty

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L003420

Multiple-Choice Questions

65. In Case 1, brain imaging was performed because:

A. The patient's presentation was incongruent with past manic episodes and she had not responded to treatment.

B. The patient's medications suggested an increased risk for an ischemic event and stroke had to be ruled out.

C. It is part of the standard inpatient workup for a patient with bipolar disorder exhibiting a manic episode.

D. It was suspected that the patient had sustained a head injury when she was detained by the police for running outside naked.

66. In Case 2, the patient's episodes of "speaking in tongues" were ultimately attributed to:

A. Residual symptoms of pre-incarceration methamphetamine use.

B. A reaction to olanzapine.

C. Brief seizure episodes.

D. Malingering in order to be removed from incarceration.

67. In Case 3, albuterol intoxication was suspected as the cause of the presenting symptoms because:

A. The lab test results indicated high serum levels of albuterol.

B. The patient admitted intentionally taking an excessive dose of albuterol.

C. The mixture of haloperidol, lorazepam, and diphenhydramine failed to reverse his symptoms.

D. The urine toxicology screen was negative for known substances of abuse and the patient was only known to have been prescribed albuterol and omeprazole.

68. In Case 4, which of the "red flags" for underlying medical conditions (mentioned in Part 1 of this lesson) does the patient's presentation include?

A. Abnormal vital signs

B. Being nonresponsive to pharmacological interventions over the last year

C. Being more than 40 years of age with no psychiatric history

D. All of the above

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Best Practices in CME

Navigating Through Psychiatric Disorders Due to Another Medical Condition: Part 2

By Vladimir Bokarius, MD, PhD, QME

ID#: L003420

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Psychiatric symptomatology is often caused directly by pathological changes in the functioning of body systems other than central nervous system. Research indicates that such potential causes of psychiatric symptoms are often overlooked by providers. As a result, the cause of some psychiatric symptoms is often misdiagnosed or not correctly identified. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), psychiatric disorders caused organically by medical illness are termed disorders due to another medical condition. The purpose of this lesson is to remind providers that mental and behavioral symptoms can be caused by organic medical conditions and may form a basis for elucidating the scope of such diagnoses and change a treatment approach.

Key Point 1: Background

Symptoms of a psychiatric disorder are not necessarily manifestations of mental illness. Don't allow your formal specialty training to preclude the performance of a differential diagnosis. Remember that many medical illnesses can cause psychiatric symptoms

Key Point 2: Evaluation & Differential Diagnosis

When evaluating a patient with psychiatric symptoms, always suspect an underlying medical condition or substance use as the cause of those symptoms until you can rule it out by taking a thorough medical and substance use history. Order any tests that may be necessary when a medical cause of symptoms of a psychiatric condition is suspected.

Key Point 3: Patient Monitoring

Monitor the patient's progress during psychopharmacological and psychotherapeutic treatment and revisit the possibility of a medical cause of psychiatric symptoms if no response is achieved with adequate trials of the selected medications. Make appropriate referrals and establish a proper follow up.

Key Point 4: Psychoeducation

Educate your patients about the organic cause(s) of their disease and the relationship to psychiatric symptoms, as well as treatment options. Reassure the patient that if they experience psychiatric symptoms beyond those caused by the medical condition, you will address them through treatment either in parallel with the medical condition or after the underlying medical condition has been stabilized.

Notes

L003421

hatherleigh

Are You Dreaming? Cognitive-Behavioral Therapy for Insomnia

Donna M. Sudak, MD; Kathy Liwski, DO; Michael Pelekanos, MD

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

KEY WORDS: Insomnia • Cognitive-behavior therapy • Sleep restriction • Cognitive restructuring

LEARNING OBJECTIVES: On completion of this lesson, the reader should be able to (1) list and define the criteria for identifying insomnia provided in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5); (2) review the benefits of *cognitive-behavioral therapy* (CBT) for insomnia; and (3) incorporate CBT-based interventions for insomnia into patient care plans.

ABSTRACT: Insomnia is a prevalent and expensive illness. Pharmacological treatments have significant limitations due to risks for addiction, lack of long-term efficacy, and risk for falls and cognitive impairment in the elderly. *CBT for insomnia* (CBT-I) is an effective alternative that does not incur such risks and conveys durability. CBT-I is a combination of clinical procedures that are carried out in the context of a warm and supportive therapeutic relationship. The sleep problem is assessed in terms of the emotions, behaviors, and thoughts that contribute to it, and sleep hygiene, stimulus control, sleep restriction, and cognitive restructuring are investigated as means of overcoming it. This lesson will review current evidence in support of CBT-I and illustrate key principles in its use.

COMPETENCY AREAS: This lesson addresses the gap in learning in the area of knowledge and patient care. Information about CBT-I is poorly disseminated; as a result, many clinicians lack an understanding of how it should be used in patient care. Upon completing this lesson, clinicians will be able to apply CBT-I principles effectively in patient care.

Introduction

Insomnia is a prevalent and costly condition with economic, mental, and physical health consequences. In the United States, $30 billion to $107.5 billion is spent on insomnia treatments each year.[1] One cross-sectional telephone survey of 7428 employed individuals revealed that insomnia costs each American worker 11.3 days of productivity each year or $2,280 in lost revenue. When controls were introduced to that study to account for comorbid medical conditions, the number of days of productivity lost decreased to 7.8 days, which is still a significant burden on the workforce. Considering the United States as a whole, these data account for an annual loss of 252.7 days of work and roughly $63.2 billion in revenue due to decreased productivity.[2]

CBT for insomnia (CBT-I) is a powerful tool that can be used to address this problem acutely and help the patient develop skills that can be used over a lifetime. This lesson is designed to familiarize the reader with CBT-I. In so doing, it will also provide a brief overview of the demographics, diagnosis, and pharmacological treatment of insomnia.

Definition and Scope of the Problem

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and the *International Classification of Sleep Disorders Third Edition* (ICSD-3)[3] provide criteria for defining and diagnosing insomnia (Table 1A-B). The DSM-5[4] defines insomnia as a disorder characterized by dissatisfaction with the quality or quantity of sleep. Such dissatisfaction is usually reported by patients as having difficulty initiating or maintaining sleep or waking too early and having difficulty returning to sleep. In addition, sleeping difficulties must cause impairment in daytime function. The difficulties must not be related to another sleep disorder or a substance (drug or medication), and the insomnia is not due to a comorbid medical or psychiatric disorder. According to the *DSM-5*, these symptoms must appear at least 3 nights per week over a minimum of 3 months and despite multiple efforts to achieve adequate sleep.[4] The *ICSD-3*[3] defines insomnia as the difficulty initiating sleep, difficulty staying asleep, and being disturbed by early morning wakening. In addition, there can be difficulty sleeping due an unreasonable bedtime, and difficulty sleeping without caregiver or parent intercession. As with the *DSM-5*, the *ICSD-3* requires the occurrence of these problems despite numerous efforts to achieve adequate sleep. The *ICSD-3* also requires a report of daytime symptoms associated with difficulty sleeping (e.g., excessive daytime fatigue, reduced energy, and labile mood, as well as daytime cognitive deficits such as impaired concentration, attention, and impaired memory).[6] *ICSD-3* mentions three categories of insomnia, chronic insomnia, short-term insomnia, and other insomnia disorder. Chronic and short-term insomnia differ by the duration of symptoms, chronic insomnia symptoms must appear at least 3 days per week over a minimum of 3 months. When the criteria for chronic or short-term insomnia are not met, "other insomnia disorder" is used as a diagnosis.

Etiology, History, and Prevalence

Estimates of the prevalence of insomnia differ from study to study, most likely because of variations in clinical criteria used to define the condition, populations used as study samples, time periods used in each study, and methods of data collection.[5] As a result, estimates of prevalence vary widely (5%-50%). [7] Population studies demonstrate, however, that nearly one third of adults report at least one night-time symptom of insomnia (difficulty falling asleep, staying asleep, or waking up too early/having non-refreshing sleep).[8-10] The prevalence of daytime symptoms that affect functioning is estimated between 10% and 15%,[10] and 10% to 20% of individuals experience chronic insomnia that greatly impairs their quality of life.[11] Based on *DSM-5* diagnostic criteria,[4] it has been estimated that roughly 6% to 10% of individuals meet the diagnostic criteria for insomnia.[4-5] **An international survey revealed that the population with the highest rate of insomnia (56%) is in the United States,** followed by Western Europe (31%) and Japan (23%).[12] The differences among prevalence rates demonstrate the need for concrete clinical criteria to define insomnia and standardized methods of data collection to better understand its epidemiology.[5]

Risk Factors

Insomnia is more common among females, the elderly, and people with lower education levels, mental health disorders (depression and anxiety), and certain medical conditions (asthma, cancer, hypertension, obesity, rheumatoid arthritis, headaches, and fibromyalgia).[13] It tends to vary among racial groups.[14] In the National Sleep Foundation's *2010 Sleep in America Poll*,[15] African-Americans reported losing sleep over life stressors at night (financial and employment worries) but reported needing fewer hours of sleep during the week to have a productive work day, and Latinos reported losing sleep over financial, employment, interpersonal, and medical concerns. Asians reported the least difficulty sleeping.[16] Insomnia increased with age in all racial/ethnic groups.[15] The limitations of studies of the prevalence of insomnia among racial/ethnic groups lie in their study design. Most are cross-sectional studies. A greater variety—and number—of studies are needed to better understand why the prevalence of insomnia differs among racial groups.[14]

Pathophysiology

The pathophysiology and etiology of insomnia involves primarily genetic, environmental, behavioral, and physiological factors (hyperarousal).[16] Research has shown that hyperarousal—which includes stimulation of the peripheral and central nervous systems, as well as an increased metabolic rate—plays a major role. Additionally, increased activity, most notably increased beta activity, has been found in encephalographic studies.[17-18] Cognitive behavioral factors also play a role. Stress may alter a person's sleep routine, generally for brief periods. In vulnerable individuals, disruption of the sleep routine persists, and cognitive and behavioral factors make the insomnia worse. Sleep-disturbing factors include ruminating thoughts about getting enough sleep, excessive napping, and altering the bedtime to ensure adequate time to sleep. These strategies usually backfire, however, and perpetuate insomnia. The bedroom becomes a place that provokes anxiety and worry instead of the tranquility needed to promote sleep.[17]

Case Example: Ms. C

Ms C is a 28-year-old, first-year investment banker working in international bond trading. She works 12-hour shifts and has tight, high-pressure deadlines. She has been obsessed with the amount and quality of her sleep, anxious about her ability to manage client portfolios effectively, and afraid that if she cannot fall asleep, her work performance will suffer. She frantically tries to nap in advance of her evening shift when she believes she has not slept enough, even when she is not tired. As she tosses and turns in bed trying desperately to sleep, she becomes so overwrought that sleep is not possible. She has been going to bed at 7 pm on nights when she is not working, to the detriment of her social life, exercise regimen, and ability to finish work-related reading. She has become highly sensitive to noise and temperature and anything that could potentially interfere with her sleep. When she does fall asleep, she generally stays asleep for only 4 to 5 hours, during which time she wakes up and feels anxious about work. She has considered staying in bed throughout the day on weekends to get enough rest. She has had several instances of similar sleep problems in the past in novel or stressful situations, although never to this degree of severity. She has no history of mood disorder or other anxiety disorders.

Assessment and Diagnosis

To obtain a thorough patient history, the physician may have to ask patients complaining about insomnia to keep a sleep diary (Table 2A-B).[19] This could provide data about the patient's sleep and demonstrate the effect that the patient's behavior is having on the quality of sleep. Sleep diaries are usually completed in the morning and in the evening. In the morning, patients log bed times, the number of times they wake up and how long they remain awake, the time they got out of bed in the morning, and how they feel in the morning. In the evening, they should record the number of caffeinated beverages consumed during the day and when they were consumed, when they exercised and the duration of exercise, medications, naps, mood throughout day, and activities performed one hour before the scheduled bed time (e.g., reading, using a cell phone, bathing, or practicing relaxation techniques).[20]

Table 2A:
Sleep Diary Upon Waking

Table 2A Sleep Diary: Complete on Waking (Sample)							
Start Date: _____	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day of the week							
Bed time							
Morning wake-up time							
Falling asleep was: a. Easy b. Took some time c. Difficult							
No. of wakenings during the night							
Total number of hours slept							
Sleep was disturbed by:							
When waking up, did you feel: a. Refreshed? b. Slightly refreshed? c. Fatigued?							

Adapted from National Sleep Foundation.[19]

Further assessment of the sleep problem involves an exploration of the patient's beliefs about sleep, how long the patient has had the sleep problem, and how the patient has attempted to manage the insomnia. Medical and psychiatric conditions that produce poor sleep, as well as other primary sleep disorders, must be assessed. The clinician should determine how the problem affects the patient during the day by asking the patient to describe a typical workday and how s/he believes the sleep disorder affects performance, mood, alertness, and activity. The physician should also determine the patient's bed time routine and how the patient behaves when s/he cannot sleep. The patient should be asked what exacerbates and relieves insomnia symptoms, including sleeping location or day(s) of the week. This information can be used to conceptualize the patient's insomnia.

Diagnostic modalities such as polysomnography are rarely used to diagnose insomnia disorder, but are mainly used to diagnose other sleep disorders.[21]

Case Conceptualization and Goal Setting:

Case conceptualization involves the interplay among (1) the degree of arousal that occurs around sleeping; (2) thoughts and behaviors that worsen the sleep problem (including behavioral disturbances such as napping, spending excess time in bed, having an irregular sleep schedule, curtailing activities in order to have more time for sleep, errors in thoughts regarding the consequences of inadequate sleep, worry about sleep, and hypervigilance over things that could disrupt sleep); and (3) subsequent daytime consequences of inadequate sleep, including performance impairment, mood disturbances, and fatigue. Once a clear concept of the patient's sleep problem has been developed, a potentially effective treatment plan can be developed, one in which sleep hygiene, stimulus control, sleep restriction, and cognitive restructuring are evaluated as means of identifying and managing the specific area(s) of concern for the patient.

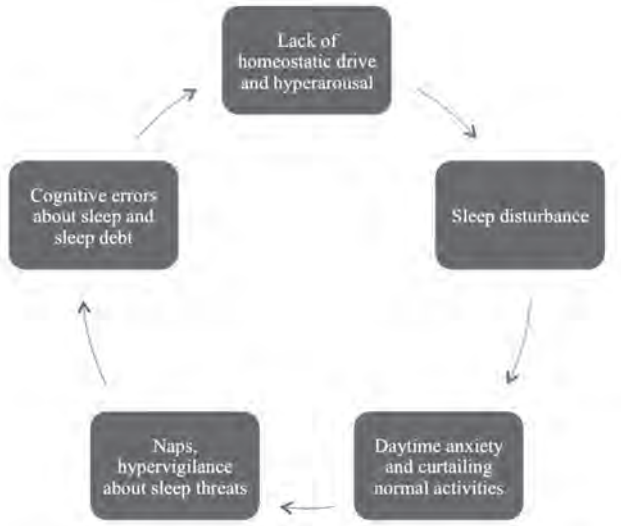
Table 2B:
Sleep Diary at End of Day

Table 2B Sleep Diary: Complete at the End of the Day (Sample)							
Start Date: _____	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day of the week							
No. of caffeinated beverages: a. Morning b. Afternoon c. Evening							
Exercise time (minutes): a. Morning b. Afternoon c. Evening							
d. Medications taken during the day							
Time spent napping (hours)							
During the day, how likely were you to doze off while performing daily activities? a. No chance b. Slight chance c. Moderate chance d. High chance							
Mood during the day: a. Very pleasant b. Pleasant c. Unpleasant d. Very unpleasant							
What did you consume 2-3 hours before going to bed?							
Activities performed 1 hour before scheduled bed time							

Adapted from National Sleep Foundation.[19]

An important component of early treatment for insomnia consists of setting goals and addressing expectations. Patients often believe that they should be "knocked out" when they go to sleep and that normal sleep involves falling asleep instantaneously. Most patients do not complain of being sleepy but instead complain of being fatigued. They frequently underestimate the amount of time that they sleep. Of key importance is the need to address maladaptive sleep habits and ideas the patient has when s/he does not have a good night sleep. Among the goals the patient should be encouraged to strive toward are (1) to decrease distress about not sleeping, and (2) to develop a sense of control over insomnia.

Figure 1:
Ms C—Case Conceptualization



Treatment

Pharmacotherapy:

The goal in prescribing medications for insomnia (Table 3) is to have the patient use them for the shortest period of time possible. Most individuals use these medications for extended periods of time because of malingering symptoms or as prophylaxis against future sleep disturbances. Additionally, in an attempt to gain the full benefit of hypnotic medications, patients tend to maximize the dose. The extended use of high doses of these medications can lead to tolerance. Thus, when they discontinue these agents, they may experience withdrawal symptoms, such as rebound insomnia. Although rebound insomnia is not a chronic condition, it may last for a few nights, thereby increasing the patient's anxiety about sleep and perpetuating the belief that sleep will only occur with the use of medication. This may facilitate the development of a psychological dependence on drugs.

Encouraging patients to discontinue sedative hypnotics can be particularly challenging. The clinician may try to educate them about the side effects and the risks associated with using them over extended periods of time. That may encourage some patients to discontinue sedative hypnotic medications out of concern over long-term side effects and the desire to sleep naturally. Those who use medications and still experience symptoms of insomnia may benefit not only from discontinuing the medication but also from a referral for another treatment modality. One method for discontinuing medications successfully involves a stepwise approach.[22-23] This approach may begin with a low-intensity intervention, such as reading an educational pamphlet or attending an educational meeting. If this approach is ineffective, the patient could be gradually introduced to more intensive interventions, such as a formal tapering program. If tapering is unsuccessful, then it may be provided in conjunction with CBT-I.[24]

When a patient agrees to taper the medication, s/he must understand that it is important to work closely with a healthcare provider in planning the process. A written plan will help with compliance. It should include the number of weeks it is expected to take for cessation to be completed if the dose is decreased by 10% to 25% every week. The patient should be introduced to the concept of medication-free nights, on which the smallest of a tapered dose is taken. Ideally, medication-free nights should be scheduled without concern for any events or activities occurring in the patient's life at that time. The number of medication-free nights should be increased over subsequent weeks. By scheduling medication-free nights on pre-selected nights, the healthcare provider prevents the patient from using the medication in response to having difficulty sleeping. If scheduled doses or complete cessation induces anxiety, the patient should be taught coping mechanisms and told that the small doses prescribed during the tapering period will have little effect on the overall quality of sleep.[24]

Table 3:
Medications Prescribed for Insomnia[25,26]

Medication Class	Medication Examples	Benefits	Side Effects
Benzodiazepines (hypnotics)	• These include flurazepam, temazepam, triazolam, and quazepam • Alprazolam, clonazepam, lorazepam, and diazepam are approved for anxiety, but have been used off-label for insomnia	• Initiate sleep quickly • Help individuals relax by reducing anxiety and muscle tension	• Falls • Sleepwalking • Excessive daytime fatigue • Delirium • Amnesia • Respiratory drive suppression • Tolerance and dependence
Non-benzodiazepine hypnotics	• Zolpidem • Zaleplon • Eszopiclone	• Per DEA, these medications are less addicting than the benzodiazepines • These medications still have abuse potential	• Daytime fatigue • Headache • Dizziness • Worsening depression or suicidal thoughts • Auditory, visual, and tactile hallucinations and delusions (esp with zolpidem and eszopiclone)
Antihistamines	• Diphenhydramine • Hydroxyzine • Doxylamine	Reduced potential for: • Abuse • Dependence • Severe respiratory depression	Anticholinergic side effects, e.g.: – constipation – dry mouth – blurry vision – memory impairment • Daytime fatigue • Dizziness
Tricyclic antidepressants	• Doxepin	May help patients: • Overcome latent sleep onset • Increase total duration of sleep • Reduce time spent awake after falling asleep • Enhance quality of sleep	• Drowsiness • Depression, suicidal thoughts • Nausea • Upper respiratory tract infection • Respiratory depression
Melatonin agonists	• Ramelteon • Melatonin supplement (OTC)	• No potential for addiction or abuse • No withdrawal complications	• Fatigue • Daytime drowsiness • Nausea
Atypical antidepressants	• Trazodone • Mirtazapine	• Promotes deep sleep (slow-wave sleep) • Promotes somnolence	Increased appetite and weight gain (Mirtazapine)
Atypical antipsychotics	• Quetiapine	Sedating at low doses	Risk of: • Oversedation • Drowsiness • Metabolic effects • Extrapyramidal side effects
Orexin receptor antagonist	• Suvorexant	• Reduces latency of sleep onset • Helps maintain sleep throughout the night	Schedule IV Substance. Presents risk for: • Daytime fatigue • Psychomotor retardation • Dry mouth • Worsening depression • Suicidal ideation • Memory impairment • Sleep paralysis • Hypnagogic and hypnopompic hallucinations

DEA, US Drug Enforcement Agency; OTC, over-the-counter.

Evidence Supporting CBT for Insomnia

CBT-I is recognized as the standard of care for insomnia and is now recommended as first-line treatment by the American Academy of Sleep Medicine, National Institutes of Health, American College of Physicians, and British Association of Psychopharmacology.[27, 28, 29, 30, 31, 32, 33] One of the greatest benefits of CBT-I is that its effects are similar to those of pharmacological treatments in terms of reducing insomnia, with the added benefit of having significant durability.[33, 34] Additionally, research shows that CBT-I results in a significant decrease in the use of hypnotic medications.[35]

In 2017, van Straten found statistically significant improvements in all sleep markers following CBT-I, with the *insomnia severity index* (ISI) affected the most and with significant improvement in measures of *sleep efficiency* (SE), *quality of sleep* (PSQI), *sleep-onset latency* (SOL), and *time awake after sleep onset* (WASO).[36] A greater number of sessions, administered in either an individual or group format (rather than in a self-help format), yielded the best results. Younger participants demonstrated greater improvement in SOL compared with older individuals; individuals with psychiatric comorbidities demonstrated the greatest improvement.[37] Compared with relaxation techniques, CBT-I has shown significant benefits and improvement in patients with insomnia.[38] Long-term therapeutic effects were sustained on sleep parameters, including SOL and SE, through the end of the study and into the follow-up period.[39]

CBT-I is effective in patients with multiple medical comorbidities, including depression, posttraumatic stress disorder, anxiety disorders, chronic pain, cancer, osteoarthritis, chronic obstructive pulmonary disease, major depressive disorder, alcohol dependence, and fibromyalgia.[39, 40, 41, 42, 43] Cancer patients showed significant improvement in fatigue following CBT-I compared with armodafinil.[44] Collectively, these findings suggest that CBT-I is useful in individuals with insomnia accompanied by a wide range of medical and psychiatric conditions.

Neurobiological Effects:

Using *magnetic resonance imaging* (MRI), various investigators have found alterations in the structure and function of the brain in individuals diagnosed with *primary insomnia* (PI). Evidence shows altered brain metabolism and altered functional connectivity that suggests a state of hyperarousal.[45] Due to the altered function and connectivity networks of the brain, exposure to sleep stimuli can induce a state of hyperarousal and hyperactivity in individuals with PI. **In a recent study, Yu-Jin Lee explored the effects of five sessions of CBT-I on functional connectivity in the brain in patients with PI.** Patients were prohibited from taking medications that affect sleep. After the CBT sessions were completed, functional connectivity between the right thalamus and right superior gyrus, the left amygdala and left lingual gyrus, the left putamen and the right superior frontal gyrus, and within the left supplementary motor area was noted to be significantly decreased. By contrast, functional connectivity was significantly increased between the left caudate and left supramarginal gyrus, the left pallidum and left orbitofrontal cortex, and the left hippocampus and left frontal pole and within the right paracingulate gyrus. Changes in PSQI, SE, and WASO scores correlated significantly with changes in functional connectivity between the various brain structures.[46]

In 2017, Kim and colleagues explored the effect of CBT-1 on brain responses to pictures of sleep-related activities.[47] The response was measured in terms of changes in *blood oxygen level-dependent* (BOLD) signaling in the brain measured through functional MRI studies. Prior to the CBT-I intervention, patients with PI exhibited greater BOLD signaling in response to *sleep stimuli* (SS) in the bilateral precentral cortex, left prefrontal cortex, left fusiform cortex, and bilateral posterior cingulate cortex; these are components of the *default mode network* (DMN). After completion of a trial of CBT-I and exposure to SS, the investigators noted a significant reduction BOLD signaling in the bilateral precentral cortex and the left prefrontal cortex.

The reduction in BOLD signaling in response to SS in the right insula and the left paracentral cortex significantly correlated with clinical reports of a reduction in WASO scores. Additionally, the decrease in BOLD signaling in response to SS in the left paracentral cortex

and the increased BOLD signaling in the left parahippocampal and right middle frontal cortices correlated significantly correlated with the decrease in overall scores on the *Dysfunctional Beliefs and Attitudes About Sleep* questionnaire. The authors asserted that the changes in these areas of brain activity were due to the cognitive restructuring effect of CBT-I on the dysfunctional beliefs of individuals with PI. These findings strongly suggest that CBT-I can normalize activity in areas of the brain that previously showed hyperarousal.[47]

Effectiveness of CBT-I vs Pharmacology:

In a placebo-controlled trial of zolpidem versus zolpidem plus CBT-I, investigators found significant improvement in SOL in the CBT-I and combination therapy groups compared with the placebo group. Consistent with other studies, their findings following CBT-I indicated improvement lasting 2 weeks after treatment. SOL returned to normal (i.e., < 30 minutes of wake time) in more patients in the CBT-I group compared with the zolpidem group, and sleep efficacy improved in the CBT-I group compared with the zolpidem group.[33] In a meta-analysis of CBT-1 and pharmacological interventions, patients enrolled in the CBT-I program demonstrated a significant reduction in sleep latency, which suggests that CBT-I is as effective against symptoms of insomnia as sedative-hypnotics without producing adverse effects.[48, 49]

CBT-I Delivery Methods:

CBT-I has been provided in various ways, including group therapy, individual therapy, brief therapy, phone-delivered therapy, the internet, and self-help venues. A "stepped-care" model requiring increasing levels of expertise with increased complexity of insomnia has been developed.[50, 51] This model expands access to care by providing resources to more individuals at a lower cost through group settings or websites and by reserving practitioners with greater expertise for the most severe cases.[52]

When CBT-I was provided in group settings, it was shown to be as effective as in individual therapy, with gains persisting 3 to 12 months after completion of therapy. When selecting patients for group CBT-1 sessions, however, the clinician must evaluate the patient's beliefs about group therapy, as well as the severity of the insomnia, the expertise of the therapist, and the characteristics of the group.[53]

An evaluation of self-directed interventions showed considerable variability in outcomes. In all studies, treatment was consistently more effective when administered through telephone contact with trained therapists than through other means. Preliminary studies evaluating the use of internet-based, electronically delivered, computerized or internet based CBT-I, known as digital CBT-I (dCBT-I), provide strong evidence that this method is effective; however, additional data will be needed before dCBT-I can be considered a gold-standard approach. In a pilot study of the mobile application CBT-I Coach, investigators found no difference in the amount of homework completed or number of days on which the sleep diaries were completed. Patients utilizing a computer application demonstrated increased adherence to therapeutic interventions and a significant reduction in ISI. Guided internet-based CBT-I platforms comparing CBT interventions with placebo were also associated with improvement in ISI, SE, SOL, and PSQI.[54] Computer-assisted CBT-I significantly improved sleep quality, sleep efficiency, SOL, and ISI but did not result in significant improvement in WASO, *total sleep time* (TST), or time in bed (TIB).[53]

Treatment of Insomnia With CBT-I

Sleep Hygiene:

Sleep hygiene consists of personal habits and lifestyle choices that can affect sleep. It is commonly evaluated and then monitored to evaluate changes in the degree of insomnia over time. During this process, the patient can be taught to modify habits and lifestyle choices that interfere with sleep. This relatively uncomplicated intervention is generally not effective when used alone in patients with established insomnia. Given the availability of information about sleep disturbances and sleep habit management to the general public, patients with insomnia will often say that they have "tried everything on the list" to no avail. Improvement in sleep hygiene involves following daytime and nighttime procedures that are designed to optimize circadian and homeostatic cues for sleep. These include standardizing routines that promote

cues to sleep, using interventions that accentuate periods of wakefulness, avoiding stimulants (caffeine, nicotine, etc.) or substances that sabotage sleep (e.g. alcohol), and not giving in to the urge to nap. A wake-up routine that increases early exercise and early exposure to bright light is instituted. At bedtime, routines are suggested that can serve as a buffer between activity and bed. The bedroom must be conducive to sleep (dark, quiet, at a comfortable temperature, and free of extraneous noise). Patients should avoid going to bed with a full stomach. Finally, a "wind-down" period at bedtime should be prescribed that includes a ritual that is relaxing and involves avoidance of blue light (i.e., a computer, cell phone, or television screen) for 2 hours before bedtime. Progressive muscle relaxation (often facilitated by using YouTube or apps that the patient is instructed to pre-load and listen to with headphones to avoid the screen) can be part of the nightly "wind-down" ritual. Finally, patients must be instructed to stop watching the clock in the middle of the night.

Stimulus Control:

Stimulus control in the context of CBT-I involves training the patient to associate bed with sleep. The patient most likely to benefit from stimulus control has a history of sleeping better when not in his/her own bedroom, has a sense of tension when anticipating going to bed, or uses the bed for many activities other than sleep (e.g., reading, eating, watching television). When the patient engages regularly in activities other than sleep while in bed, the brain associates being in bed with being awake (which is the opposite of the desired effect). Stimulus control involves a series of rules about the use of the bed. The patient is assigned a strict bed time and wake-up time (go to bed and wake up at the same time every day, irrespective of the day of the week or the amount of time they slept the night before). Other activities, with the exception of sex, are prohibited, including naps. **Most importantly, if the patient is unable to sleep for 10 to 15 minutes during the night (gauged not by watching the clock, but by estimation), s/he must not stay in bed but must get up and engage in a monotonous activity in a room with low lighting. When the patient is sleepy again, s/he may return to bed.** This procedure should be repeated as often as necessary.

Stimulus control can be a challenge, especially in terms of finding a boring screen-free activity when the patient needs to get out of bed. It may be particularly problematic for individuals who are at risk for falling when they get out of bed. By far the biggest problem regarding stimulus control, however, is motivation. Often patients must consider the pros and cons of enduring the discomfort of getting out of bed in the middle of the night to be convinced that it is worth attempting.

Case Example: Ms. C:

Ms C had numerous sleep-related habits that needed correction. For example, she was keeping very irregular sleep hours, and on many nights she would lie awake with an increasing sense of frustration as she struggled to relax. She became highly sensitive to noise, temperature, and anything else that could interfere with sleep. Her solution to this was to keep the television on at a low volume in case her neighbors made any noise that might wake her. She also brought work projects into bed with her, surrounding herself with folders and papers. She has several close friends who live on the West Coast and she frequently takes advantage of the difference in time zones to call them at midnight ("it's the only thing I do for myself"). All of these habits were addressed in therapy, first by pointing out that they are understandable but would not have the desired effect (i.e., restful sleep). Ms C was very willing to keep her work out of the bed, but it was more difficult to persuade her to stop calling her friends at midnight and stop trying to "make up for lost sleep." Strategies that were helpful in persuading her to try other behaviors included asking her to plan alternative times to talk with friends and look at the effect of her irregular sleep habits on her life, as described in her sleep diary.

Sleep Restriction:

Sleep restriction is a highly potent intervention used in CBT-I. It is most effective when unreliable sleep leads to more time spent in bed in an attempt to get more sleep. This can lead to sleep fragmentation and reduce instances of deep sleep. The first step in the process of sleep restriction is to keep a sleep diary. This can be used

to estimate the average duration of sleep each night, i.e., the total time asleep divided by the number of days plus 30 minutes (the time spent falling asleep). The average duration of sleep per night divided by the time spent in bed per night represents SE. An SE of 80% to 90% means that sleep restriction may be beneficial. The patient may be instructed to reduce the amount of time spent in bed to 85% of the average total sleep time and take no naps. In this case, for example, if the patient sleeps total of 7 hours per night but stays in bed for 9 hours, she should be instructed to set the alarm so that she is only in bed for 6 hours. If she is reluctant to do so, she can start by limiting the time spent in bed to the average amount of time asleep. When she is capable of sleeping 6 hours without interruption over several days, she can gradually increase her sleep time by 15 minutes a night and continue to increase it, as long as her sleep remains unbroken.

Obviously, there are some patients for whom sleep restriction may be contraindicated, including patients with seizure disorders or those in whom it must be undertaken with great care and informed consent, including patients with bipolar disorder. If the sleep debt from restriction is profound (i.e., the patient would be limited to 5 hours of sleep per night), it is absolutely necessary to help the patient determine how to limit activities (e.g., driving) or how to manage work during that time. One challenge with sleep restriction is identifying activities that will help the person stay awake until close to bedtime that are not too stimulating. It can also be challenging to develop strategies that will motivate the patient to get out of bed, no matter how tired s/he feels. Problem-solving around these issues must occur, however.

Managing Cognition:

Typically, it is necessary to use CBT to modify and manage worry, rumination, or unhelpful beliefs about sleep. Intrusive thoughts at night and during the day must be addressed. If the patient selectively focuses on things that could disrupt sleep, an assessment of such unhelpful thoughts, through the use of traditional thought records, becomes a critical part of treatment. The patient should be taught to pay attention to thoughts that s/he has when lying awake in bed or thoughts about sleep during the

Figure 2:
Ms. C's Thought Record

Situation	Automatic Thought	Emotion	Physical Sensation	Evidence: Perspective Taking	New Thought	Outcome
Stayed out later than intended	I've blown it; I'll never get enough sleep tonight.	Anxious	Keyed up, tense	I've slept less on other nights and been OK.	Even though I was out late, I'll have enough time to get enough rest; worrying about it will backfire.	Able to settle down in about 30 minutes.
Job deadline is looming	Maybe I should pull an all-nighter; I could be too stressed to sleep.	Anxious	Keyed up, tense	Staying up all night is not likely to result in good work performance. It won't help me to dwell on the work project.	I will try some muscle relaxation exercises and wind down.	Went to bed but got up once because I was unable to fall asleep. Read some recipes for 15 minutes and then went to sleep.
Lying awake in bed	I'll never be able to sleep normally. This is terrible. Why can't I sleep like everyone else?	Frustrated	Tense	I know lots of people who have insomnia. There are nights when I get a good amount of sleep. I have survived many nights of poor sleep.	Dwelling on my insomnia is not helping me. There is no "perfect" way to sleep.	Still a little frustrated. Listened to music and eventually fell asleep.

day. Monitoring excessive worry about sleep and environmental or other factors that could interfere with sleep provides an opportunity to help the patient achieve more realistic expectations about sleep and change any ideas about the causes or consequences of inadequate sleep, e.g. worsened work performance ("I performed poorly at work today because I slept poorly"), dysfunctional or unrealistic beliefs about sleep itself ("The only way to operate effectively is to get 8 full hours of sleep") or beliefs about what someone should do if sleep does not occur in a certain way ("I must take naps to make up for poor sleep"). Occasionally, individuals have positive beliefs about worry ("Worrying at night helps me solve problems") that need to be explored. The desirable endpoint of such interventions is when the patient understands that there is no gold standard of sleep. The patient is encouraged to generate alternative interpretations of sleep by looking at the evidence and treating such ideas as hypotheses to be tested.

Summary

Sleep problems are a significant source of morbidity. There are limitations to the use of pharmacotherapy that are related both to side effects and the risk of dependency. CBT-I has been proven to be an effective alternative to pharmacotherapy. The combination of clinical procedures to be used in CBT-I is determined by case conceptualization by the clinician and subsequent treatment targets. Sleep hygiene, sleep restriction, stimulus control, and cognitive restructuring each has a place in helping patients learn how to manage their thoughts and behaviors to facilitate arousal and promote with the normal homeostatic drive to sleep. CBT-I provides tools that the patient can use whenever intercurrent stresses make normal sleep difficult. These benefits are obtained without the significant risks associated with pharmacological treatment.

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L003421

Multiple-Choice Questions

69. What is the ideal first step when encouraging patients to discontinue sedative hypnotic medications?

A. Refer to a sleep medicine specialist.

B. Offer a holistic medication.

C. Educate the patient about the side effects and risks of using medications for an extended period of time.

D. Tell the patient you will refuse to continue to write prescriptions for the medication.

70. According to one international survey, which population has the highest percentage of individuals reporting difficulty sleeping?

A. Americans

B. Western Europeans

C. Eastern Europeans

D. Asians

71. Patients exposed to ___ sessions of CBT-I showed changes in functional connectivity in the brain.

A. 2

B. 3

C. 5

D. 7

72. CBT-I has been shown to be effective in the treatment of primary insomnia in which of the following populations?

A. Major depressive disorder

B. Chronic obstructive pulmonary disease

C. Fibromyalgia

D. All of the above

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Best Practices in CME

Are You Dreaming? Cognitive-Behavioral Treatment for Insomnia

By Donna M. Sudak, MD; Kathy Liwski, DO; Michael Pelekanos, MD

ID#: L003421

This valuable take-home reference translates the research and theory that are presented in the accompanying continuing medical education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Insomnia is a prevalent and expensive illness. Pharmacological treatments have significant limitations in terms of risks for addiction, lack of long-term efficacy, and risks for falls and cognitive impairment in the elderly. CBT for insomnia (CBT-I) is an effective intervention that does not incur such risks and conveys durability. CBT-I is a combination of clinical procedures that are implemented in the context of a warm and supportive therapeutic relationship. The patient's sleep problem is assessed, and the emotions, behaviors and thoughts that perpetuate it are targeted with sleep hygiene, stimulus control, sleep restriction and cognitive restructuring.

Key Point 1: Obtain a Sleep History

Employ a sleep diary to help patients understand the effect their behavior has on sleep.

Key Point 2: Assessment

Determine what thoughts and behaviors drive the patent's insomnia and target them systematically.

Key Point 3: Employ Sleep Restrictions

Employ sleep restriction, sleep hygiene, and stimulus control to help the patient behave in ways that increase the homeostatic drive to sleep.

Key Point 4: Challenge Erroneous Thoughts

When the patient has a predominance of negative or erroneous beliefs about sleep, thought recording is an effective strategy to assist in the development of more accurate and functional ideas.

Notes

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Transgender Care: Health Care Disparities and Physician Attitudes

Cassandra A. Adduri, MD; Nareesa Ali, MD, FRCPC;
William P. Fleisher, MD, FRCPC

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

KEY WORDS: Transgender • Mental health • Physician attitudes

LEARNING OBJECTIVES: On completing this lesson, the clinician will be able to (1) define the terms "gender non-conforming" and "transgender;" (2) identify barriers to health care experienced by transgender individuals; (3) explain the mental health concerns of those who identify as transgender; (4) describe common attitudes of healthcare professionals toward transgender people; and (5) delineate recommendations for improving physician competency and compassion regarding the care of people who identify as transgender.

LESSON ABSTRACT: As the number of people who identify as transgender increases, physicians encounter a greater number of patients from that community. Unfortunately, not all physicians feel comfortable with transgender patients, possibly because of a lack of information about this population and its healthcare concerns. This lesson reviews some of the disparities in the health care needs of transgender individuals compared with the rest of the population, particularly the LBGTQ population, that suggest a need to modify medical education programs enabling clinicians with needed support to provide transgender patients competent and compassionate care.

COMPETENCY AREAS: On completing this lesson, the reader will be familiar with healthcare issues facing transgender individuals, particularly mental health concerns. The reader may also develop greater appreciation of the inadequacy of medical education programs in preparing physicians to provide optimal care for transgender individuals with sensitivity to their needs. The reader may then consider improvements in medical education to overcome these inadequacies to provide transgender patients optimal care.

Introduction

Gender nonconformity refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms associated with a particular sex.[1] Similar to "gender nonconforming" is the term "transgender," which is used to describe people who have gender identities, behaviors, or manners of expression that are not traditionally associated with their birth sex. This includes individuals who identify more strongly with another gender, e.g., the natal female who identifies as male (a *female to male* [FTM], or trans man) or the natal male who identifies as female (a *male to female* [MTF], or trans woman). Transgender also refers to individuals whose gender identity is beyond traditional dichotomous gender constructs (i.e., individuals who feel they possess both genders or neither). This is in comparison to those who are "cis gender," i.e., their gender identity corresponds with their sex at birth.

In the medical community, the word "transgender" has historically been associated with pathology. **During the 1980s, the term "transgender" was assigned to the category of Gender Identity Disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III).*[2] In the *DSM-5* (2013), it was reassigned to a "gender dysphoria," which suggests that the patient's discomfort or distress is caused by the discrepancy between gender identity and sex assigned at birth.[3]** By removing the word "disorder" the authors may have intended to convey that transgender individuals were no longer considered mentally ill. People who identify as transgender, however, believe that the inclusion of gender dysphoria in the *DSM-5*[3] perpetuates the belief that having a transgender identity is a sign of mental illness.[4] In an effort to reduce this stigma, the World Health Organization recently modified the *International Classification of Diseases* by moving the term "gender incongruence" (previously called "gender dysphoria") from its chapter on mental disorders to its chapter on sexual health.[5, 6]

This lesson begins with a description of the size of the transgender community in the United States and Canada. It then reviews healthcare challenges in this community and mental health concerns. The attitudes of physicians toward these patients are then explored, and, finally, recommendations for improving both attitudes toward transgender patients and competencies in addressing their healthcare needs are discussed.

How Many People Identify as Transgender?

Recent (2016) estimates of the size of the transgender population suggest that 0.6% of adults in the United States (approximately 1.4 million people) identify as transgender;[7, 8] that is approximately twice the number estimated in a 2011 survey. **The reported increase in size of the transgender population may be due to the fact that a greater proportion of the general population has become aware of them and this, in turn, may have led to the decision to use more sophisticated methods of data collection. Growing social acceptance of transgender people may have led to the willingness of a greater number of individuals to identify themselves as transgender on surveys.** In Canada, the estimated proportion of the population that identifies as transgender is slightly lower than in the United States (0.5%),[9] despite growing awareness of this population. This may reflect the fact that the transgender population is still one of the more marginalized populations. It has frequently been investigated as part of the *lesbian, gay, bisexual, transgender, and questioning/queer* (LGBTQ) community. This can be problematic, because individuals who identify as transgender face unique barriers in the healthcare system and may face a greater stigma than other members of the LGBTQ community.[10] For example, a 2013 survey of 2000 heterosexual Americans revealed significantly less favorable attitudes toward transgender individuals compared with lesbian, gay, or bisexual individuals.[10] In a 2011 National Transgender Discrimination survey of more than 6000 transgender and other non—gender-conforming individuals in the United States, transgender respondents were twice as likely to report being mistreated as often as lesbian, gay, and bisexual respondents.[11] This finding is particularly important, in that it demonstrates the difficulty in distinguishing the healthcare needs of the transgender population separately from the LGBTQ population. This difficulty may be due, in part, to limitations in the design of research tools.

Healthcare Challenges to Those Who Identify as Transgender:

Individuals who identify as transgender have reported challenges in accessing competent health care and feeling discriminated against when they attempt to obtain health care. In a 2005 survey carried out in Philadelphia, Pennsylvania, approximately 26% of the transgender respondents reported being denied health care when they disclosed that they were transgender.[12] Similar results were reported the same year in Chicago, where 14% of the transgender individuals interviewed reported being denied emergency health care and 3% reported being denied mental health care.[13] According to the 2014 Trans Pulse project, which reported the findings of a survey of 400 transgender individuals in Ontario, Canada, 29% of the respondents reported being unable to obtain emergency care when needed, and 21% reported not seeking medical care because of concern over how they would be treated because of their transgender status.[14]

In the 2011 US National Transgender Discrimination Survey of 6450 transgender and gender non-conforming individuals, 50% of respondents reported having to teach their medical providers about transgender care, 33% reported postponing preventive care appointments because of the expectation of discrimination, and 28% reported postponing medical care even when they were sick or injured because of concern over how they would be treated.[11] Additionally, 28% reported experiencing verbal harassment in a physician's office, and 19% reported being refused medical care because of their transgender status. Most (90%) of the transgender respondents believed there are not enough medical personnel who are properly trained to care for them, and 52% worried about being refused medical services when they need them.[11] In a 2010 US national survey distributed to LGBT people and people living with HIV nationwide (n= 4916), 20.9% of transgender respondents reported being subjected to harsh language from healthcare providers, 20.3% reported being blamed for their own health problems, 15% reported that healthcare professionals refused to touch them or used excessive precautions, and 7.8% reported experiencing physically rough or abusive treatment by a medical provider.[15]

If transgender individuals do not feel comfortable seeking medical treatment because they expect to be stigmatized, harassed, or humiliated, their health conditions—particularly their mental health—could deteriorate further.

Mental Health Concerns

Transgender individuals reportedly experience depression at a higher rate than in the general population and are at an increased risk of suicide.[16, 17, 18, 19] In the United States, for example, approximately 41% of transgender individuals have attempted suicide, compared with 2% of the general U.S. population.[20] Individuals who experienced gender dysphoria before undergoing gender-affirming surgery may be at increased risk of suicidal ideation, suicide attempts, and completed suicides.[20]

In Canada, the prevalence of depression among transgender women or MTF individuals (n = 191, with approximately 34.2% in the process of medical transitioning through surgery or hormone therapy, 22.7% had completed all hormonal or surgical changes, approximately half were currently using feminizing hormones, and one in five had undergone at least one transition-related surgery) in Ontario was 61.2% and even higher among those living outside Toronto. The risk of depression was also increased among transgender women who had some postsecondary education, were unemployed, or had experienced trans phobia (as defined by the authors as experiencing societal discrimination against those who do not conform to traditional gender norms) more frequently than others. Approximately 36% of the transgender population reported having suicidal thoughts during the previous year; of these, 10% had attempted suicide. Not surprisingly, children and those who had experienced trans phobia or perceived a lack of support were at an increased risk of committing suicide.[21]

In 2018, a study was carried out in the United States, to compare the mental health of 1300 transgender and gender non-conforming children (aged 3-17 years) with that of their cis-gender peers. There has been past research in gender development in the general population that supports the idea that gender-typed behavior can be noticeable from the ages of 3-8, hence the relatively young age of examining this population.[22, 23] Electronic Medical Health records information (from California and Georgia) was used to identify a cohort 1333 transgender individuals (ages 3-17 years old). This cohort was matched to a total of 13 151 cis gender reference males and 13 149 cis gender reference females. **In children**

aged 3 to 9 years, the most common mental health disorders were *attention deficit disorder* (ADD; trans feminine: 15%; trans masculine: 16%) and anxiety disorders (trans-feminine: 12%; trans-masculine: 16% children). In the adolescent group (aged 10-17 years), the prevalence of ADD and anxiety disorders was also high (trans-feminine: 25%; trans-masculine: 16%), but the most common diagnoses were characterized by depressive symptomatology (trans-feminine: 49%; trans-masculine: 62%).[24]

Attitudes of Medical Students Toward Transgender People:

One of the largest studies (N= 1700) of the attitudes of medical students toward the LBGT community revealed that these attitudes were generally favorable, although students who identified themselves as lesbian, gay, or bisexual (n = 200) were significantly more likely to express a positive attitude toward this patient population than the others. Despite the high percentage of positive attitudes reported, only 12.9% of the medical students received a passing score on a test of their knowledge of the medical concerns of these patients. Again, students who identified themselves as lesbian, gay, or bisexual were more likely to receive a passing score than the others.[25]

In a similar study in Canada, more than 95% of medical school students (n= 155) indicated that they felt that transgender issues were important and should be addressed by physicians, yet only 10% of these students felt comfortable about treating transgender individuals.[26] Virtually no change in these attitudes was detected after the students participated in a program that focused on health issues of concern to the transgender community. The study investigators hypothesized that this lack of effect was due, at least in part, to the program not being well taught, as reported by many of the students who participated in it. In other studies, investigators found that medical education that focuses on transgender issues improves the comfort level of healthcare professionals who will be treating transgender individuals.[27, 28, 29, 30, 31, 32, 33] Per the Canadian study, the quality of the teaching must be taken into consideration.

Does Transgender-Related Medical Education Correlate With Comfort Level Among Clinicians Who Will Treat Transgender Patients and Improve Their Attitudes Toward Them?

Many studies of the effect of medical education on the physician's comfort with transgender patients and sense of competency with transgender-specific health issues have used small sample sizes. Despite this limitation, the consensus is that medical education that addresses transgender issues improves the comfort level of medical students and residents treating transgender individuals. Boston University School of Medicine developed a transgender medicine elective, which included rotations through services in which transgender patients were seen for care. In 2018, Park and Safer interviewed 20 medical students who had participated in this program and found that their comfort with these patients and confidence in their ability to treat them appropriately improved significantly as a result of participating in this program.[34] The University of California in San Francisco developed a similar program, one consisting of six online medical education modules addressing transgender patient needs in fourth-year medical students, pediatric and psychiatry interns and nurse practitioners. After completing this program the participants reported that they felt their knowledge of transgender related health issues and their sensitivity to transgender individuals had improved over the course of the program.[35] This demonstrated that as little as 2 hours of instruction can improve attitudes and help healthcare providers improve their clinical skills—importantly, their history-taking skills—with transgender individuals.[35]

In a 2017 survey of internal medicine residents (N = 67), 97% reported that they believed transgender health issues are relevant to their practice, but only 45% had been educated regarding these issues. Most of the survey participants reported that they did not feel up to date on screening guidelines that are relevant for transgender patients; however, they did identify higher rates of depression and suicide as key issues in that population.[36] In the previous year, Ali and colleagues reported that psychiatry residents and staff psychiatrists (N = 142) generally had fewer negative attitudes toward transgender patients

compared with undergraduate controls and that their attitudes correlated with clinical exposure to transgender individuals.[37]

Kidd and colleagues (2016) developed a 90-minute workshop for PGY1 to PGY4 psychiatry residents, designed to (1) increase the residents' empathy toward and respect for the diverse life experiences of transgender patients; and (2) increase their awareness of the need to consider gender identity and expression when working with transgender patients. During the first 10 minutes of the workshop, key concepts such as sex, gender, gender identity, transgender, societal sex roles, and sexual orientation were defined (Table 1). During the remainder of the program, the participants (N = 22) were provided questions they could ask patients to determine their gender identity and determine the name and pronoun by which the patient wanted to be referred. The residents were then divided into groups to role-play relevant clinical scenarios; these were carried out with a facilitator. Compared to baseline (i.e., the period prior to participation in the workshop), the participants reported a significant increase in empathy, knowledge, and comfort with transgender patients, as well as motivation for post-workshop learning. Ninety days after the workshop, the investigators found no significant difference in these qualities compared to baseline. This suggests that ongoing education involving multiple clinical exposures may be more effective than a single workshop in helping residents learn how to provide clinically competent and compassionate care to transgender patients and in reinforcing a positive professional attitude toward this population.[38]

Attitudes of Practicing Physicians Toward Transgender Individuals

Multiple studies suggest that regardless of the number of years of training or clinical exposure, physicians feel uncomfortable treating transgender patients and believe that they lack the knowledge required to treat them effectively.[27, 28, 29, 30, 31, 32, 33] Unfortunately, the literature on physician attitudes toward transgender people specifically is lacking. Ali, Erickson, and Fleisher [2017, personal communication] used the *Gender Trans Phobia Scale* (GTS)[39] to survey 149 residents and staff physicians in the Departments of Psychiatry, Pediatrics, and Emergency Medicine at the University of Manitoba, Canada. Their responses to the GTS (which assesses attitudes towards transgender individuals) revealed that the **physicians who identified as female, had a liberal political ideology, or expressed less religiosity than the others were more likely to have a positive attitude toward transgender people than the other physicians who participated in this survey**.

In a recent survey of endocrinologists, investigators found that despite having more education and training in this area than other practitioners, the majority of these healthcare professionals rated their competency in providing care for transgender patients as low, only half felt comfortable discussing gender identity and/or sexual orientation, and more than one-third refused to provide transgender patients hormonal care.[40] A recent survey of obstetrics-gynecologists revealed that only one-third felt comfortable caring for transgender patients and that the majority did not know the recommendations for breast cancer screening in MTF patients.[41] The failure of the in-depth education and training provided to these specialists to instill confidence in their knowledge and comfort with the transgender population and its health concerns reinforces the need for transgender-specific information and exposure to help physicians develop competency in and comfort with transgender patient care.

Recommendations

In 2015, the *American College of Physicians* (ACP)[42] published a position paper with recommendations for addressing disparities in healthcare needs within the LGBT population. These recommendations—particularly for working with the transgender community—are discussed in this section.

One of the first steps toward developing compassion for transgender patients is to bear in mind that in their community, gender is not viewed as a fixed, dichotomous variable classified into two categories (male or female), as it is the general population. Public and private healthcare plan administrators should also keep this in mind when updating their policies to include coverage of medical services that are relevant to the transgender community.

It is also critical to understand that the issue of gender identity is separate from that of sexual orientation. Just as sexual orientation is covered under Civil Rights laws in many jurisdictions, the issue of gender identity should be addressed in the antidiscrimination and anti-harassment policies of every medical institution. Physicians should be

expected to be capable of gathering pertinent information about both gender identity and sexual orientation when taking a history from a transgender patient.

Every medical facility should allow each patient to determine who may visit them and who may act on their behalf during their stay, regardless of their sexual orientation, gender identity, or marital status, which should be encouraged with transgender patients. It would also be helpful to encourage more members of the LGBT community to enter the field of medicine and offer programs that support LGBT medical students, residents, and practicing physicians as they advance in their careers.

The ACP also encourages the development of data collection and research methodologies that can help us advance our understanding of the demographics of the LGBTQ population, identify potential causes of LGBTQ health disparities, and develop best practices for reducing these disparities. The need for research addressing health issues in the transgender community is urgent, given that transgender patients may face barriers to health care that differ from those faced by lesbian, gay, or bisexual patients.

Transgender Health and Medical Education

The following issues may be key to the development of competence and compassion in the care of transgender individuals:

1. **Medical schools, residency programs, and continuing medical education programs should incorporate LGBTQ-related health topics into their curricula. Transgender health, for example, should be taught in medical school as a clinical competency. A one-time educational intervention may improve clinicians' attitudes in the short-term,[38] but when transgender health is presented as a core competency that is taught several times during medical school and as part of the programming for residents, the effect is much more long-lasting.**

2. **Traditional educational interventions (e.g., lecture, seminars, workshops, etc.) should be central to the development of transgender health competency[27, 43] and accompanied by the development of policies designed to reduce discrimination against—and, thus, stigmatization of—transgender patients. The educational efforts may require supervised clinical training exposure to transgender individuals. This will enhance the experiential learning needed by physicians to develop their interpersonal skills with this patient population.**

3. **Core competencies in LGBTQ-related health issues should continue to be taught in medical school and expanded to include transgender-specific needs. In so doing, it may be necessary to distinguish among the needs for trans men, trans women, and non-binary individuals. For example, training in internal medicine may need to emphasize the differences in health screenings required for trans men versus trans women.**

4. **Medical students and residents should be taught how to take a history from transgender individuals; this process should be done under observation. At least part of this training could take place in a simulated learning environment in which medical students can practice treating someone who is transgender. Carefully observed and evaluated role-playing may further promote the development of this skill and help physicians develop their interpersonal skills further.**

Conclusion

Despite the rising number of people who identify as transgender, healthcare providers remain uncomfortable with the idea of providing them care and making them feel comfortable enough to seek care. The basis of this problem is the lack of physician confidence in their ability to address transgender-specific health issues and in their interpersonal skills with this population. These barriers can be overcome by adjusting medical school and residency training programs to provide cognitive and experiential learning regarding transgender health care. Changes are also needed in healthcare systems, hospitals, and community-based settings to ensure that members of the transgender community are treated equally under the law and receive competent and compassionate medical care.

Table 1:
Terms of Reference

Cis-gender	Identified by the gender that was assigned at birth
Gender expression	The outward manifestation of gender identity, e.g., clothing, hairstyle, voice, body shape (usually referred to as masculine or feminine)
Gender identity	The internal sense of being female, male, neither, or both For transgender people, gender identity may differ from the sex assigned at birth
Sex assigned at birth	Classification of the individual as male, female, intersex, or other usually on the basis of anatomy and/or karyotyping
Sexual orientation	The individual's attraction to others based on their physical, romantic, emotional, esthetic, and/or other characteristics In Western cultures, gender identity and sexual orientation are not the same
Transgender/Trans	The individual whose gender identity differs from the sex assigned at birth The term "transgender" does not indicate gender expression, sexual orientation, hormonal makeup, physical anatomy, or how one is perceived in daily life
Transition	The process of developing and assuming a gender expression that matches one's gender identity Transition can include coming out to one's family, friends, and co-workers; changing one's name/sex on legal documents; receiving hormone therapy; and possibly (although not always) undergoing surgery
Transsexual	The transgender individual who desires medical assistance to transition from one gender to another
Face/masculinization	Surgical reshaping of feminine facial features into more masculine features This surgery can be of interest to both trans men (FTM) and cis-gender males who want to appear more masculine.
Top surgery	In FTMs: double mastectomy and chest contouring for a more masculine appearance In MTFs: Use of saline or silicone implants to achieve a more feminine appearance
Bottom surgery	Vaginoplasty: surgical construction of a vaginal cavity between the rectum and urethra Phalloplasty: surgical construction of a functioning penis from a flap of skin taken from the forearm Metoidioplasty: surgical construction of a neophallus using existing genital tissue. It can be performed when testosterone intake results in considerable clitoral growth

FTM, female-to-male
MTF, male-to-female

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L003422

Multiple-Choice Questions

73. What is the difference in classification of the term "transgender" in the *DSM-III* versus *DSM-5*?

A. Gender dysphoria was reclassified as gender incongruence.

B. Gender dysphoria was reclassified as gender identity disorder.

C. Gender identity disorder was reclassified as gender dysphoria.

D. Gender incongruence was reclassified as gender dysphoria.

74. Why has the number of people identifying as transgender increased?

A More awareness and social acceptance.

B. More sophisticated data collection in identifying those who are transgender.

C. Increased comfort levels in identifying as transgender.

D. All of the above.

75. All of the following may influence the chance that a physician will have a positive attitude toward transgender patients, *except*:

A. Being female.

B. Being male.

C. Having a liberal political ideology.

D. Expressing less religiosity.

76. All of the following as associated with medical students having a more positive attitude toward transgender individuals, *except*:

A. Identifying oneself a lesbian.

B. Identifying oneself as gay.

C. Identifying oneself as bisexual.

D. Identifying oneself as female.

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Best Practices in CME

Transgender Care: Health Care Disparities and Physician Attitudes

By Cassandra A. Adduri, MD; Nareesa Ali, MD, FRCPC; William P. Fleisher, MD, FRCPC

ID#: L003422

This valuable take-home reference translates research and theory that are presented in the accompanying continuing medical-education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

This lesson reviews some of the disparities in the health care needs of transgender individuals compared with the rest of the population, particularly the LBGTQ population, that suggest a need to modify medical education programs to provide clinicians with needed support enabling them to provide transgender patients competent and compassionate care.

Key Point 1: Background Information

Transgender is used to describe people who have gender identities, behaviors, or manners of expression that are not traditionally associated with their birth sex. It is estimated that 0.5% of the population in the United States identifies as transgender, and in Canada 0.4% of the population identify as transgender.

Key Point 2: Mental Health Concerns

Transgender individuals experience a higher rate of depression and are at increased risk of suicide when compared to the general population. In transgender children (ages 3-9), the most common mental health disorders were attention deficit disorders and anxiety disorders, however in adolescents (ages 10-17) the most common mental health diagnoses was of depressive symptomatology (49-62%), similar to what is found with adults.

Key Point 3: Factors Improving Attitudes Toward Transgender Individuals

Physicians who identified as female, had a liberal political ideology, or expressed less religiosity compared to others were more likely to have a positive attitude towards transgender patients.

Key Point 4: Education

More education starting in medical school is required to improve physician's attitudes and in turn improve transgender care. Transgender health should be taught as a clinical competency taught several times a year, and should include supervised clinical exposure training to transgender individuals.

Notes

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Aggression in Children and Adolescents: Pharmacological Strategies

Tina Gurnani, MD; Jeffrey H. Newcorn, MD

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

KEY WORDS: Aggression • Disruptive behavior • Conduct • Pharmacological treatment • Children

LEARNING OBJECTIVES: Upon completing this lesson, the clinician will be able to (1) recognize pathological aggression and its risk factors; (2) summarize treatment guidelines that focus on aggression in children and the similarities among these approaches; and (3) describe the systematic approach to medication management in children with aggression, taking into account the safety and efficacy of each treatment, as well as their limitations based on current evidence.

LESSON ABSTRACT: Aggression is one of the most common reasons for referring children and adolescents for psychiatric care. Aggression accompanies a wide range of psychiatric disorders and carries a high risk of poor outcomes. Recently, several studies revealed evidence in support of pharmacotherapeutic intervention, especially in children with impulsive aggression. Medications that have demonstrated positive effects in children with this disorder include psychostimulants, α-2 agonists, mood-stabilizing agents, and atypical antipsychotics. In this lesson, we review diagnostic considerations, the literature guiding treatment choices, and consensus guidelines for the treatment of aggression in children, thereby providing a step-wise approach to the use of medications in children with aggression accompanying various conditions.

COMPETENCY AREAS: This lesson presents information clinicians can use to review subtypes of aggression in children and risk factors for aggression. It also demonstrates the application of recent guidelines in the treatment of patients with aggression from a pharmacological point of view and will enable clinicians to develop an approach to the management of aggression across a range of disorders.

Introduction

Aggressive behavior has been reported in approximately 10% to 25% of children and constitutes one of the most common reasons for referring them for psychiatric services.[1] Children with aggressive behavior often demonstrate profound disturbances in a range of functional domains, including academic and occupational attainment, social and family relationships, and psychological development. Aggression is commonly a target of both psychosocial and pharmacological therapy, but the urgency of the condition often dictates the selection of the latter. Given the dearth of child and adolescent psychiatrists, a significant number of prescriptions for these children that were provided between 1995 and 2002 were written by clinicians other than mental health professionals.[2] This has raised a considerable amount of concern over drug efficacy and safety, as well as polypharmacy.[3] This lesson provides an overview of evidence-based recommendations to guide clinicians in the implementation of appropriate therapeutic interventions in children with aggression.

Aggression is a behavioral construct that is present to some extent in everyone. In clinical cases, it is pathological, persistent, and highly impairing. Prosocial or adaptive aggressive behaviors (i.e., self-defense) must be distinguished from pathological, maladaptive, or antisocial aggressive behavior. Maladaptive aggression may occur in the absence of specific triggers, and its intensity, frequency, duration, or severity is out of proportion with its causes. By contrast, pathological aggression occurs as a component of a specific psychiatric disorder or as a nonspecific manifestation of anger or frustration.

Clinically, the various levels of aggression are commonly distinguished by the individual's motivation, ability to control the behavior, and intended goal. *Impulsive aggression* (IA) is generally reactive, unplanned, and overt, with the aggressor perceiving the outcome in a negative light. *Planned aggression* (PA; i.e., predatory, instrumental aggression) is often covert. It may be associated with a negative emotion, but the aggressor anticipates a positive outcome**. IA is more likely than PA to be seen in clinical cases; fortunately, it is more amenable to pharmacological and psychosocial treatment**. By contrast, PA is more likely to appear as a characteristic of delinquency. While these descriptors are often conceptualized as dichotomous, IA/reactive and PA can be displayed by the same individual. Using an aggression scale to measure reactive/impulsive and proactive/planned aggression, investigators recently found that the scores for these two conditions are distinct but correlate moderately with each other.[4] Children with PA may benefit from psychosocial intervention; however, pharmacotherapy has not traditionally been considered effective in these patients unless IA is also present. Callous-unemotional traits (which are generally thought to be related to PA) have also been studied with respect to behavioral problems in children, in whom they seem to be associated with higher rates of aggression,[5] especially proactive aggression.[6, 7] Distinct domains of aggression may be associated with distinct neurobiological mechanisms and treatment indicators. In adults, for example, IA has been associated with low serotonergic functioning or reactivity in adults. Data are less consistent in children, however, and do not offer clear directives for the approach to pharmacotherapy in this age group.[8]

Risk Factors

Risk factors for IA may develop at an early age, often as early as age 4 or 5 years (compared with age 6-7 years for PA);[9, 10] thus, it is sometimes necessary to treat young children. Because transient disruptive behaviors are common during the preschool years, it is important to distinguish pathological aggression from variations in normal development. Young boys are especially prone to aggression; this gender bias is consistent worldwide. Girls tend to exhibit more covert aggression than boys and less intense behavioral disturbances. Early aggression is a key predictor of later delinquency, however;[11] approximately half of school-aged children who exhibit aggressive behavior continue to do so through adolescence.

Childhood trauma has repeatedly been shown to predict violent behavior later in life, with cumulative exposure to trauma associated with increased risk. Sexual abuse may also be a risk factor for aggression,[12] as well as parental separation and conflict, poverty, harsh discipline, and parental criminality. Other risk factors include friendship with delinquent peers, living in a high-crime neighborhood, witnessing community violence, and peer rejection.[13] The large number of environmental, familial, and social contextual factors associated with a risk for

aggression underscores the importance of psychosocial treatment. Interestingly, poor peer relationships and a history of physical abuse are often associated specifically with IA, whereas aggressive role models in the family and parental incarceration have been associated with overt aggression.[8] A low IQ and poor language skills are additional risk factors for early and persistent disruptive behaviors.[14] Presumably, the range of adaptive skills in children with poorly developed language skills is restricted.

Clinical Approach

Treatment plans for aggressive children are based on a comprehensive understanding of the nature, severity, and context of symptoms. Psychological, behavioral, developmental, and cognitive factors must be considered, as well as the profile of risk and protective factors that characterize the patient and the patient's family. The likelihood of consequences (e.g., harm to self or others) that could arise from these aggressive behaviors is also taken into account. In emergent situations, especially situations in which the child or adolescent has already caused injury to others or has access to means of inflicting harm, hospitalization and/or acute pharmaceutical intervention using sedative agents may be necessary.

In the less emergent outpatient setting, there are two general approaches to aggression in children: (1) a symptom-based approach (i.e., empirical treatment of aggressive symptoms), or (2) treatment of the underlying disorder (assuming one can be identified—which is not always the case). The current consensus is to first treat aggression in the context of a specific disorder using pharmacotherapy that targets the underlying condition.[15] The most common underlying conditions are *attention-deficit/hyperactivity disorder* (ADHD) and disruptive behavior disorders, including *conduct disorder* (CD) and *oppositional defiant disorder* (ODD), especially in younger children.[16] Of note, ADHD and *disruptive behavior disorders* (DBDs) are often comorbid. Mood disorders and neurodevelopmental disorders are also commonly accompanied by aggression, as are posttraumatic stress disorder, *autism spectrum disorder* (ASD), and *intellectual disability* (ID). Other potential underlying conditions include anxiety disorders, tic disorders, specific learning disorders, and adjustment disorders. A medical work-up may be required to rule out exposure to toxins, seizures, infections, head trauma, and substance use.

Several guidelines have been developed for the treatment of aggression in children that are based on both clinical research findings and expert consensus. The *Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth* (TRAAY) guidelines indicate that psychosocial treatment is, in most cases, the cornerstone of a first-line intervention. Medications are generally used as the next step and should target the primary underlying disorder, e.g., stimulants for ADHD and *selective serotonin reuptake inhibitors* (SSRIs) for depression or anxiety.[17] Other key steps in the TRAAY guidelines include avoiding polypharmacy when possible and offering an atypical antipsychotic when psychosocial measures and first-line medications fail. The antipsychotic should initially be administered at a low dose and titrated gradually so the patient can continue taking it for at least 2 weeks at an adequate dose before it is considered ineffective. Crisis intervention strategies should be used to minimize the need for emergency chemical and physical restraints, and patients should be evaluated routinely for side effects to ensure that an adequate trial has been completed before the medication is switched or combined with other medications. If the trial was ineffective, the patient may be switched to a different atypical antipsychotic. The clinician may consider adding a mood stabilizer to the therapeutic regimen if the patient only exhibited a partial response to the first antipsychotic, **tapering the medications if the patient exhibits an inadequate response to multiple agents, or tapering the antipsychotic medications that do not produce an adequate response within 6 months.** Recently, the Center for Education and Research on Mental Health Therapeutics developed *Treatment of Maladaptive Aggression in Youth* (T-MAY), a similar set of guidelines for primary care clinicians and mental health providers to guide their approach to children and adolescents who exhibit aggressive behavior. Key recommendations in T-MAY are to start with evidence-based parent and child skills training then treat the underlying disorder that is believed to have given rise to the behavior, taking into careful consideration the potential risks and contraindications for the initiation of medications while avoiding polypharmacy and closely monitoring treatment response and medical side effects.[18]

Treatment of Aggression in the Context of Specific Psychiatric Disorders

ADHD and Disruptive Behavior Disorders:

Psychostimulants comprise the most effective pharmaceutical therapy for patients with ADHD, producing a mean *effect size* (ES) of 0.8 to 1.0. An abundance of data shows that stimulants generally reduce aggression in children with ADHD. According to one meta-analysis,[16] these effects are especially evident in patients exhibiting overt or covert aggression (ES: 0.84 and 0.69, respectively). Stimulants are also often effective in patients exhibiting symptoms of ODD and often reduce symptoms of CD in children with comorbid ADHD, regardless of the severity of ADHD.[19, 20, 21] Thus, **stimulants are first-line agents for the pharmaceutical treatment of patients exhibiting aggression in the context of ADHD and DBD**. Even in children thought to be demonstrating an inadequate response to stimulants, retitration to an optimal dose of *methylphenidate* (MPH) or *amphetamine* (AMP) may increase improvement in many.[22]

Unfortunately, a substantial proportion of children with ADHD-associated aggressive behavior do not respond sufficiently when treated with a stimulant.[15] Even when there is a positive response, treatment with stimulants is limited by their relatively short duration of action (even the current long-acting formulations) and the possibility of rebound symptoms when the medication wears off. Because aggression can be present at any time of the day, treatments that last all day are highly desirable.

Nonstimulant medications such as *atomoxetine* (ATX) and the extended-release formulation of α-2 adrenergic agonists have been approved by the *US Food and Drug Administration* (FDA) for use in patients with ADHD and are effective against core symptoms. Their benefits in individuals with ADHD-associated aggression have been less well studied than those of stimulants, despite their extensive use in clinical settings for aggressive behaviors (particularly α-2 agonists). The findings of some studies suggest that both clonidine and guanfacine can be helpful in reducing the severity of symptoms of ODD in children with ADHD.[23, 24] Clonidine has also been shown to reduce aggression in adolescents with ADHD,[25] and guanfacine has been shown to increase frustration tolerance and decrease irritability[26] in adolescents with IA. Data for ATX have thus far shown that it can induce modest improvements in pediatric aggression[17] and ODD comorbid with ADHD.[27] Thus, ATX may not be the best choice for a first-line agent.

Antipsychotics, especially second-generation agents, have frequently been used for aggression associated with ADHD.[28] Several studies of their efficacy have revealed that antipsychotics should ideally be used with stimulants (e.g., Findling et al. 2000; Armenteros et al., 2007).[29, 30] They have not been approved by the FDA specifically for this purpose, however, and should be used with caution. The recent double-blind, randomized, placebo-controlled *Treatment of Severe Childhood Aggression* (TOSCA) study of antipsychotics in combination with other treatment strategies in children with ADHD and ODD/CD who exhibit severe physical aggression revealed that antipsychotics could be effective as a therapeutic augmentation strategy when a first-line treatment (stimulant medication + parent training for behavioral management) produces suboptimal improvement or causes deterioration. The agents evaluated in this trial included risperidone. At the end of 9 weeks, the risperidone group demonstrated moderate improvement in aggression ratings,[31] especially in ratings of IA and disruptive behavior, as opposed to callous PA.[32] There is some evidence that combination therapy using a stimulant and an atypical antipsychotic may be helpful for controlling callous-unemotional traits in children with CD, which is more difficult to treat and generally thought to have a poorer prognosis.[33] Quetiapine has been studied infrequently and primarily in open-label trials (e.g., Kronenberger et al., 2007)[34] in combination with MPH in patients with aggression associated with ADHD comorbid with ODD or CD. In a recent Cochrane review of 10 randomized, placebo-controlled studies of antipsychotics prescribed for disruptive behavior (8 of which investigated risperidone), risperidone was found to reduce aggression and conduct problems. The investigators indicated, however, that larger and longer-term studies are needed.[35] In a study of quetiapine[36] and another study evaluating unpublished data for ziprasidone, these drugs were associated with significant rates of attrition. Each of these studies used a small sample size, however. Overall, it is believed that additional *randomized controlled trials* (RCTs) are needed, especially for other atypical antipsychotics. The design of

such studies may be challenging because of concern over the effects of long-term use of these drugs, primarily their metabolic side effects. In the TOSCA study, for example, children who received risperidone gained an average of 2.37 kg more than the placebo group over a period of 6 to 10 weeks. Furthermore, concomitant use of stimulants and antipsychotics does not seem to combat the metabolic effects of antipsychotics, contrary to speculation.[37]

There is a long history of using mood stabilizers to control aggressive behavior disorder in children. In a seminal study carried out in 1984 to compare the effects of lithium and haloperidol in treatment-resistant hospitalized children,[38] investigators found that both medications were superior to placebo in reducing behavioral symptoms, but haloperidol had a more sedating effect. Subsequent studies of lithium have supported this finding, although the effect size was lower (e.g., Campbell et al., 1995; Malone et al., 2000).[39, 40] Valproic acid has also demonstrated efficacy in ameliorating aggression in children with ADHD; studies are limited, however.[41] Valproic acid produced response rates superior to those of placebo in a preliminary crossover study in children with ODD/CD who demonstrated an explosive temper or mood lability. In an RCT of this drug in adolescent juvenile offenders with CD, higher doses of valproic acid yielded greater improvement in clinician- and self-reported ratings of impulse control compared with lower doses.[42, 43] In a more recent small study, an 8-week regimen of divalproex (vs placebo) to augment behavioral therapy was evaluated in children with ADHD comorbid with ODD/CD in whom aggressive behavior persisted after treatment with a stimulant had been optimized. Children who received divalproex had significantly higher rates of remission compared with placebo.[22] Those with an inadequate response to stimulant monotherapy exhibited increased irritability and mood dysregulation initially. More studies are needed to better characterize the role of mood stabilizers in these patients compared with antipsychotics and other medications.

Intellectual Disability and Developmental Disorders

Aggressive behavior is often seen in children with an ID or ASD. In the past, medication for these conditions was often prescribed off-label, particularly atypical antipsychotics.[44] Because of this, and because of preliminary findings indicating beneficial effects with risperidone in this population,[45, 46, 47] more definitive studies were conducted to obtain FDA approval for this application. In 2002 and 2004, two double-blind, placebo-controlled RCTs of risperidone conducted in children with autism and DBD demonstrated significant improvements in irritability, based on the *Aberrant Behavior Checklist* (ABC)—Irritability subscale after 8 weeks of treatment.[48, 49] In a 6-month double-blind, placebo-controlled RCT, investigators observed a reduction in irritability and aggression in children with autism.[50] In a 24-week, multisite RCT comparing risperidone monotherapy (subjects could be switched to aripiprazole if ineffective) with the combination of risperidone and parent training therapy, investigators found that combination therapy was somewhat more effective than medication alone with a 14% lower dose of risperidone at the end of the study.[51] **In a more recent study, Politte and McDougle (2014) reported improved ratings of aggression with aripiprazole with similar or slightly lower response rates than are typically seen with risperidone.[52] Both medications were subsequently approved by the FDA for this indication and are now considered first-line choices in this population unless other concerns (i.e. an adverse side-effect profile) dictate otherwise.** There is insufficient evidence that other antipsychotics, such as olanzapine and quetiapine, are as effective as risperidone or aripiprazole against aggression in patients with developmental disabilities, although both medications are approved for bipolar disorder in adolescents and presumably might yield benefit in these populations.

Beta-blockers are often prescribed off-label for children with ID and have produced positive results in several studies. Unfortunately, no RCTs have been carried out to determine their effects on aggression.[53] Nonstimulant medications for ADHD, such as clonidine and guanfacine, have also been used, particularly when hyperactivity/impulsivity and sleep problems are present. Additionally, mood-stabilizing medications have been prescribed off-label to reduce aggression in children with developmental disabilities. In a small, placebo-controlled study of divalproex versus placebo in children and adolescents with ASD, a 12-week course of the study drug reduced irritability/aggression compared with placebo.[54]

Mood Disorders

Behavior problems and aggression are encountered more frequently in children with depressive disorders than

in adults. For example, children with depression have a higher risk for CD.[55] Serotonergic and noradrenergic antidepressants may decrease impulsivity and aggression in these patients.[56] For example, fluoxetine was associated with a significant reduction in *Modified Overt Aggression Scale* (M-OAS) scores in a double-blind RCT in 100 adults with intermittent explosive disorder and concurrent IA.[57] Low serotonergic activity early in life has been associated with high levels of aggression, risk taking, and premature death in nonhuman primates. The role of serotonin in childhood aggression is less clear—in some studies, investigators have observed high serotonergic reactivity, whereas in others, they found low reactivity.[8] Thus, treatment of depression with SSRIs may reduce aggression,[58] provided the patient has not demonstrated long-standing difficulty with such behavior. The use of SSRIs or other antidepressants to control aggression in children and adolescents in the absence of depression is not currently recommended.

The medical literature addressing aggression in pediatric bipolar disorder cases is expanding. In several studies, divalproex was shown to reduce aggression in manic bipolar adolescents (e.g., DelBello et al., 2004) and those at high risk for bipolar disorder.[59, 60] Less evidence exists for other anticonvulsants, e.g., lamotrigine. Lithium, which has been approved by the FDA for use in children aged 12 to 18 years with bipolar disorder, generally ameliorates aggression and irritability in these children.[61] The need to monitor serum lithium levels may limit its use in these populations, however. Antipsychotics such as risperidone, quetiapine, aripiprazole, olanzapine, and asenapine have also been approved by the FDA for use in adolescents with bipolar disorder; lurasidone has been approved specifically for use in adolescents with bipolar depression. In some studies, specific agents have been shown to be effective specifically against aggressive behaviors. In a study of divalproex versus quetiapine in children with impulsivity and reactive aggression comorbid with bipolar disorder and ODD/CD, investigators found that these two medications were similar in efficacy. Unfortunately, neither study used a placebo control group.[62] In a case series involving adolescents with aggression refractory to other mood stabilizers, the addition of risperidone to their medication regimen was followed by a reduction in the severity of aggressive behavior.[63] In a prospective double-blind, placebo-controlled RCT, adolescents with bipolar disorder comorbid with DBD and aggression exhibited a greater reduction in manic symptoms with risperidone compared with divalproex than adolescents with bipolar disorder without comorbidity.[64] Additional data for other antipsychotics against aggression in bipolar adolescents are lacking.

Psychotic Disorders

In adolescents with psychotic disorders such as schizophrenia, antipsychotics serve as first-line treatment, even when the disorder is not associated with aggression. In several studies (e.g., Kumra et al., 2008),[65] this class of medications has shown efficacy in the control of schizophrenia spectrum disorders. TRAAY Guidelines and the American Academy of Child and Adolescent Psychiatry practice parameters recommend the use of antipsychotic medication for this population, typically a second-generation agent.[17, 66]

Symptom-based Therapeutic Approach to Aggression

Limited research supports the use of medication when the primary underlying disorder has not been identified, in part because of the heterogeneity of aggressive symptoms and difficulty in assessing aggression reliably. Atypical antipsychotics are being prescribed with increasing frequency under these conditions, including by primary care providers. IA is thought to be most amenable to pharmacotherapy. Recent research has indicated a positive response to pharmacotherapy in patients with other aggression subtypes, as well. Further research is required, however. For example, little is known about the response of pediatric patients with CD and callous-unemotional traits to pharmacotherapy. It has been presumed that medication is not useful in children with these disorders, even though recent data suggest a similar response in children with ADHD-associated aggression who are treated with stimulants, whether callous-unemotional traits are present or not.[67] This finding may seem counterintuitive, but it is instructive. Given that many children with callous-unemotional traits also show features of IA, treatments that target IA symptoms may play a role in this population.

Assessment of Aggression in Children

The assessment of aggressive behavior in children involves a multi-step, multi-informant approach. The clinical assessment usually begins with an interview of the patient and his/her family, although it is also essential to obtain collateral information from teachers and other adults. The mental status exam is also informative because it can be used to assess cognitive-emotional capacities, including verbal skills, affect regulation, and the capacity for empathy. A careful evaluation of the latter capacities can be useful in determining the potential for a response to treatment.

Psychometric instruments are also informative for clinical evaluation and monitoring treatment (Table 1). The *Conners' Parent and Teacher Rating Scales, Child Behavior Checklist, ABC*, and *Nisonger Child Behavior Rating Form* have aggression subscales, in addition to scales to gather general information about behavior and functioning relating to age and gender norms. Narrow-band scales such as the *Children's Aggression Scale, M-OAS,* and *Buss-Durkee Hostility Inventory* provide more specific data regarding the context, severity, and precipitants of aggression. These are often used in research, but they can also be helpful in the clinical setting, especially when evaluating covert aggressive behaviors. The *Young Mania Rating Scale* is specific to mania but can be used to monitor aggression in the context of bipolar illness. When aggression is a prominent symptom but the primary diagnosis is difficult to identify, it may be useful to distinguish between impulsive and premeditated aggression (because IA is more likely to be amenable to pharmacotherapy) and select behaviors that occur frequently enough to be monitored for a need to change treatment. The *Impulsive/Premeditated Aggression Scale* has been validated in adolescents and young adults and has been used to differentiate aggressive behaviors among adolescents with CD.[80] The usefulness of this instrument in monitoring treatment response has not been evaluated; however, it can be helpful in establishing baseline characteristics of aggression in children and guide decisions regarding treatments that affect impulsivity, regardless of diagnosis. The *Antisocial Behavior Scale* (ABS) is used to distinguish between reactive/impulsive aggression and proactive aggression.[79] The ABS has been validated in clinical cases and was recently used in the TOSCA study.[68, 69, 71, 72, 73, 74, 75, 76, 78]

Other objective tools—such as neuropsychological testing to assess response inhibition, consequence sensitivity, startle response, and psychophysiological measures of autonomic sensitivity—can be useful for characterizing domains of aggression and/or impulsivity but are not sufficient to diagnose IA. Neuropsychological testing and consequence sensitivity evaluation can provide important information about underlying cognitive processes related to risk, as well as the capacity to utilize behavioral treatment successfully. The other assessment tools are best reserved for the research setting.

Safety Considerations and Monitoring of Pharmacotherapy

Medications for aggression should be used judiciously and with close patient monitoring, given potential safety concerns. With regard to psychostimulants, the potential for slightly delayed weight and growth attainment, as well as cardiovascular risk, has been debated extensively, primarily because growth trajectory is not a major issue in the majority of adolescents and there is usually no evidence of an elevated risk for sudden death or other potentially serious cardiac outcomes.[81, 82] A baseline *electrocardiographic* (ECG) reading is not essential before treatment, although it is suggested for patients with arrhythmias, hypertension, structural cardiac defects, or a family history of cardiac events. α-2 adrenergic agonists are associated with changes in heart rate, blood pressure, and QTc interval. Sedation and changes in vital signs usually resolve throughout treatment, however, and QTc changes are small and do not lead to significant adverse events. ATX carries a rare risk for liver toxicity. Routine liver function testing is not generally recommended before initiating treatment, however, although a thorough work-up is indicated in patients with related symptoms or at risk for them. ATX and antidepressants carry an FDA black box warning for suicidal thinking in individuals younger than 25 years of age; therefore, close patient monitoring is recommended when treatment begins and when there is a change in dosing. Of particular concern recently is the safety profile of antipsychotics in adolescents. Typical antipsychotics may induce extrapyramidal symptoms, and atypical antipsychotics may cause weight gain, metabolic syndrome, and hyperprolactinemia. In one systematic review of antipsychotics prescribed for

Table 1:
Assessment of Aggression in Children

Scale	Description	References
Child Behavior Checklist	Parent report of ADHD, ODD, and CD symptoms and other symptoms. Ages 6-18 years	Achenbach et al., 1991;[68] Achenbach and Rescorla, 2001[69]
Conners Parent and Teacher Rating Scale	Parent, teacher, and self-reports of ADHD, ODD, and CD symptoms. Full-length or short version. Ages 6-18 years (8-18 y for self-report). Third edition updated per DSM-V	Conners et al., 1998[70]
Aberrant Behavior Checklist	Originally designed to assess problem behaviors in ID. Contains 6 subscales: irritability/agitation/crying, lethargy/social withdrawal, stereotypic behavior, hyperactivity/noncompliance, and inappropriate speech. Rated by informant (parent, teacher, case worker, etc.)	Aman et al., 1985[71]
Nisonger Child Behavior Rating Form	Parent or teacher report. Separate version for children. Used to evaluate intellectual/developmental disabilities and normal development. A "Typical IQ Version" is now available	Aman et al., 1996;[72] Tassé et al., 1996[73]
Children's Aggression Scale	Parent and teacher rating forms. Frequency and severity of aggression in children aged 5 to 18 years. Contains 5 domains: verbal aggression, aggression against objects and animals, provoked physical aggression, unprovoked physical aggression, and use of weapons. Distinguishes aggression (1) inside vs outside the home and (2) against children vs adults	Halperin et al. 2002;[74] 2003[75]
Modified Overt Aggression Scale (M-OAS)	Suitable for outpatient settings. Rates behavior over 1 week. Measures 4 domains of aggression: verbal, aggression against property, autoaggression, and physical. 5-point response format allows assessment of both severity and frequency and weighted scoring	Sorgi et al. 1991[76]
Buss-Perry Hostility Inventory	Self-report. Originally developed for college students. Modified for children with items updated to eliminate those not relevant to children and improve readability for children with relatively low vocabulary skills	Buss and Perry 1992[77]
Impulsive/Pre-meditated Aggression Scale	Self-report. Half of the items correlate with impulsive aggression, the other half with premeditated aggression	Stanford et al., 2003[78]
Antisocial Behavior Scale	Originally a 28-item teacher rating scale distinguishing proactive vs reactive aggression. Recently validated for parent reports in clinical samples	Brown et al., 1996[79]

ADHD: attention-deficit/hyperactivity disorder
CD: conduct disorder
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ODD: oppositional defiant disorder
ID: intellectual disability

adolescents, the investigators found an increased risk for type 2 diabetes mellitus in a younger patient group.[83] Typical and atypical antipsychotics are heterogeneous in terms of their potential for inducing cardiometabolic conditions. Several of these agents are known to present a risk for an increase in heart rate and corrected QT interval on ECG that may progress to a torsades de pointes arrhythmia in susceptible individuals. It has been suggested that patients for whom these medications are prescribed should be evaluated for neuromotor effects (e.g., using the *Abnormal Involuntary Movement Scale*), as well as heart rate, blood pressure, and liver function every 3 months and annually. Additionally, height, weight, body mass index, lipid profile, and fasting glucose should be evaluated at 3 months then every 6 months; ECG should be evaluated during titration; and prolactin levels should be checked if symptoms develop.[84] Safety concerns have also been associated with mood stabilizers used for aggression, primarily valproic acid and lithium. Lithium serum blood levels should be monitored because of its narrow therapeutic window to prevent toxicity. Lithium may also inhibit or stimulate thyroid function, the latter effect usually reversing when the drug is discontinued. Valproic acid also has a mild antithyroid effect; therefore, a thyroid

function test should be administered at baseline and after 1 to 2 and 6 to 12 months of treatment with either drug.[85] Lithium can also affect renal function, causing acute toxic effects, nephrogenic diabetes insipidus, or chronic renal dysfunction; for this reason, regular monitoring is indicated.[86] Valproic acid can cause renal tubular injury; thus, in addition to metabolic monitoring, periodic urinalysis may be warranted. There is also a potential for pancreatitis and blood dyscrasias. Therefore, baseline and regular monitoring of platelets and a complete blood count are recommended, as well.[87, 88]

Conclusion and Clinical Significance

Treatment of children and adolescents with aggression is a very high priority because of the high risk of poor outcomes, including delinquency, substance abuse, and the continuation of aggression and antisocial behavior into adulthood. A number of evidence-based options are available that are generally best considered in the context of a differential diagnosis. Disruptive and aggressive behaviors are often refractory (or partially refractory) to medication, whether it is administered as monotherapy or combination therapy. This is most often true for patients with early and severe symptoms, comorbidity, and multiple psychosocial risk factors. It is essential to distinguish IA from more overt or planned aggression, which may be less amenable to pharmacotherapy, and utilize medications in the context of multimodal interventions. Several psychosocial treatments have an established evidence-based effect on aggression in adolescents; these include caregiver behavioral management techniques, anger management/modifying techniques, academic optimization, and collaboration among family, school personnel, and care providers. Pharmacotherapy for IA is generally targeted for the primary disorder and often with success. In refractory cases, it may be beneficial to switch to another agent or combine medications, e.g., with atypical antipsychotics or mood stabilizers. According to current guidelines (i.e., TRAAY and T-MAY), systematic trials of effective medications—e.g., 2 weeks of treatment with a single medication before switching to another agent—while monitoring symptoms systematically to document improvement is recommended. Polypharmacy should be avoided as much as possible, and drug withdrawal should be avoided until after the crisis has abated or after a 6- to 9-month period of remission.

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L003423

Multiple-Choice Questions

77. Medication may have the most benefit for which of the following types of aggression?

A. Covert

B. Antisocial

C. Planned

D. Impulsive

78. A 9-year-old boy with ADHD and ODD has been displaying frequent aggressive behavior that has his teachers and parents concerned. For which of the following medications has there been the most evidence of its value as a first-choice monotherapy?

A. Stimulants

B. Atomoxetine

C. α-2 agonists

D. Antipsychotics

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Best Practices in CME

Aggression in Children and Adolescents: Pharmacological Strategies

By Tina Gurnani, MD; Jeffrey H. Newcorn, MD

ID#: L003423

This valuable take-home reference translates the research and theory that are presented in the accompanying continuing medical education lesson into a systematic review of the lesson's key points for easy assimilation into your armamentarium of knowledge and daily practice.

CME Lesson Overview

Referral for aggression in children and adolescents is common in psychiatric practice. In some instances, the nature of the aggression necessitates treatment beyond psychotherapeutic interventions. Therefore, there has been an increasing push for guidelines on effective medication treatments. Various studies have recently been conducted across a wide range of psychiatric disorders which can present with childhood aggression, and include medication classes such as stimulants, alpha-agonists, mood stabilizers, and antipsychotics. As a result, systematic expert guidelines have been developed, outlining the recommended steps of treatment and safety considerations, which underscore the importance of psychosocial measures as first-line treatment, defining associated diagnoses, using medications targeting specific conditions where possible, avoiding polypharmacy, and offering a trial of antipsychotic medications in certain refractory cases.

Key Point 1: Assessment

Determine if the nature of the aggression is pathological and if the acuity dictates medication treatment. Distinguishing between IA (impulsive aggression) and PA (planned aggression) can be a key factor in selecting medication treatments in certain disorders.

Key Point 2: Approach to Treatment

Guidelines emphasize the importance targeting treatment towards the primary diagnosis if known. Disruptive behavior disorders, including ADHD, are the most common underlying conditions associated with aggression in children and adolescents. Mood disorders and neurodevelopmental disorders are often associated as well.

Key Point 3: Selecting Medication Treatments

Stimulants, as well as non-stimulants such as alpha-2 agonists, can be effective in reducing pediatric aggression in ADHD, ODD, and CD. Antipsychotics can be beneficial alone or in combination with these medications if a patient's response is inadequate. In other disorders, such as autism, clinical trials have led to FDA approval of certain antipsychotic medications for irritability and aggression. For psychotic disorders, antipsychotics are considered first-line treatment. SSRIs may reduce aggression in children and youth with depressive disorders; while in bipolar disorder, divalproex and risperidone have the most data.

Key Point 4: Limitations

In many instances, especially in children with disruptive behaviors and severe aggression, medications may yield unsatisfactory results or partial response. Psychotherapeutic interventions are often essential in such cases, and switching to another pharmacological agent may be required. Further, medication side effects, such as the potential for metabolic syndrome with antipsychotics, may limit use in certain populations. Following parameters for monitoring is recommended. Although the literature base for the role of medications to treat childhood aggression is expanding, studies may be limited by sample size, lack of a placebo group, or other factors, which should direct future goals of investigation.

Notes