Directions in Psychiatry

CATEGORY 1
AMA PRA
Credit Hours
CME

VOLUME 35

VOLUME 35 * LESSONS 1 – 20 * IN THIS VOLUME

1 — *CME LESSON 1*
Neurodevelopmental and Environmental Hypotheses of Negative Symptoms of Schizophrenia
Frédéric Limosin, MD, PhD

13 — *CME LESSON 2*
The Place of Psychotherapy in Contemporary Psychiatry
Saman Tavakoli, MD

25 — *CME LESSON 3*
Exploring Psychosis and Bipolar Disorder in Women: A Critical Review of the Qualitative
Anja Wittowski, Laura K, Mcgrath, and Sarah Peters

43 — *CME LESSON 4*
Bipolar Disorder in Children, Part 1: An Overview
Kimberly Renk, PhD; Rachel White; Brea-Anne Lauer; Meagan Mcswiggan Jayme Puff; and Amanda Lowell

61 — *CME LESSON 5*
Bipolar Disorder in Children, Part 2: Assessment and Interventions
Kimberly Renk, PhD; Rachel White; Brea-Anne Lauer; Meagan Mcswiggan Jayme Puff; and Amanda Lowell

79 — *CME LESSON 6*
Behavioral Activation for Depression
Donna M. Sudak, MD; and M. Khalid Zafar, MD

93 — *CME LESSON 7*
The Changing Landscape of Care: Does Ethics Education Have a New Role to Play in Health Practice?
Julie Wintrup

107 — *CME LESSON 8*
Effects of Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea on Cognitive Functions: Evidence for a Common Nature
Georgia Andreou, Filippos Vlachos, and Konstantinos Makanikas

133 — *CME LESSON 9*
Narcissism in DSM-5 Section III Model for Diagnosis of Personality Disorder
Elsa Ronningstam, PhD; Igor Weinberg, PhD

151 — *CME LESSON 10*
Internet Addiction: Comorbidity with Psychiatric Disorders
Aviv Weinstein, PhD

163 — *CME LESSON 11*
Treating Insomnia
Vladimir Bokarius, MD, PhD; and Simon N. Ferber, MA

183 — *CME LESSON 12*
The Mental Health Sequelae of Major Disasters
Carol S. North, MD, MPE

199 — *CME LESSON 13*
Preventing Retraumatization in Mental Health Settings in Women with Serious Mental Illness
Lauren Mizock, PhD

213 — *CME LESSON 14*
Adjunctive Pharmacological Agents in the Treatment of Schizophrenia
Dimitrios Kontis, MD, PhD; Eirini Theochari, MD; and Michael S. Ritsner, MD, PhD

229 — *CME LESSON 15*
Psychiatric Disorders and Psychotropic Treatment in the Postpartum Period
Asim A. Shah, MD; Awais Aftab, MD; and Samantha Latorre, MD

247 — *CME LESSON 16*
Depression: An Overview and Diagnostic Changes in the DSM-5
Ali M. Hashmi, MD; and Asim Shah, MD

263 — *CME LESSON 17*
From Dementia to Neurocognitive Disorders: DSM-5 Changes
Nidal Moukaddam, MD, PhD; and Asim Shah, MD

279 — *CME LESSON 18*
Cognitive Impairments in Alcohol-Dependent Subjects
Florent Bernardin, Anne Maheut-bosser, and François Paille

293 — *CME LESSON 19*
Narcolepsy as an Immune-Mediated Disease
Alberto K. De la Herrán-Arita, MD, PhD; and Fabio García-García, PhD

305 — *CME LESSON 20*
Pediatric Pain Assessment and Management: A Systematic Approach Including Psychiatric Assessment
Lindsay A. Thompson, MD, MS; Michelle Chaney-Catchpole, MD, MScPH; and Caprice Knapp, PhD

Directions in Psychiatry

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Accreditation Statement

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

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Learning Objectives Evaluation Form

Directions in Psychiatry, Vol. 35

Full Name: _____ **Date:** _____ **Customer No:**_____

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

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

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

CME Lesson 1: Neurodevelopmental and Environmental Hypotheses of Negative Symptoms of Schizophrenia

____ examined the role of environmental factors which are often implicated in the course of schizophrenia in adults.

____ considered how certain psychosocial and biological factors have shown an increased risk of them developing schizophrenia.

CME Lesson 2: The Place of Psychotherapy in Contemporary Psychiatry

____ recognized that psychotherapy is still a very relevant part of clinical psychiatry.

____ considered the necessity to develop evaluation methods to measure the effectiveness of psychotherapy.

CME Lesson 3: Exploring Psychosis and Bipolar Disorder in Women: A Critical Review of the Qualitative Literature

____ reviewed of the literature concerning women's experiences with psychosis and bipolar disorder.

____ appreciated why they should be more sensitive as they encounter such patients in their daily work and treatment planning.

CME Lesson 4: Bipolar Disorder in Children, Part 1: An Overview

____ reviewed the historical background of bipolar disorder in the literature.

____ compared and contrast the development of diagnostic criteria included in the *Diagnostic and Statistical Manual of Mental Disorders.*

CME Lesson 5: Bipolar Disorder in Children, Part 2: Assessment and Interventions

____ reviewed recommendations for assessing bipolar disorder in children.

____ reviewed psychosocial and medication treatment interventions when managing bipolar disorder alone as well as with comorbid psychiatric disorders.

CME Lesson 6: Behavioral Activation for Depression

____ been able to define and describe behavioral activation

____ better understood how to implement activity scheduling with depressed patients.

CME Lesson 7: The Changing Landscape of Care: Does Ethics Education Have a New Role to Play in Health Practice?

____ examined the way ethics education is designed in a changing healthcare environment.

____ considered how ethics education that promotes moral agency, rather than problem solving approaches, would explore not only clinical problems, but also the difficult and contested arenas in which they occur.

CME Lesson 8: Effects of Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea on Cognitive Functions: Evidence for a Common Nature

____ reviewed the defining symptoms of *chronic obstructive pulmonary disease* (COPD) and *obstructive sleep apnea syndrome* (OSAS).

____ examined symptoms in COPD and OSAS and their impact on cognitive function.

CME Lesson 9: Narcissism in DSM-5 Section III Model for Diagnosis of Personality Disorder

____ reviewed the DSM-5 Section III hybrid dimensional and trait-focused diagnosis for narcissistic personality.

____ considered how to apply a collaborative, exploratory diagnostic strategy that identifies the range of narcissistic personality functioning, fluctuating self-esteem, and the co-occurrence of both self-enhancing grandiosity and self-depleting vulnerability.

CME Lesson 10: Internet Addiction: Comorbidity with Psychiatric Disorders

____ reviewed recent evidence on the assessment, diagnosis, and comorbidity of Internet addiction.

____ reviewed the evidence on the relationship between Internet addiction and comorbid psychiatric disorders and the development of these disorders.

CME Lesson 11: Treating Insomnia

____ recognized the necessity of treating insomnia.

____ identified the full spectrum of currently available medications for treatment of insomnia.

Learning Objectives Evaluation Form

Directions in Psychiatry, Vol. 35 (cont.)

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

CME Lesson 12: The Mental Health Sequelae of Major Disasters

____ reviewed the types of mental-health sequelae that can be expected in the wake of disasters,

____ differentiated between psychiatric disorders such as *posttraumatic-stress disorder* (PTSD) and stress.

CME Lesson 13: Preventing Retraumatization in Mental Health Settings of Women with Serious Mental Illnesses

____ identified the risks for trauma and retraumatization among women with serious mental illnesses.

____ recognized the challenges faced in detecting, assessing, and diagnosing trauma-related psychiatric conditions.

CME Lesson 14: Adjunctive Pharmacological Agents in the Treatment of Schizophrenia

____ summarized current and older evidence concerning the role of compounds used to enhance the efficacy and tolerability of antipsychotics in schizophrenia.

____ understood that the available antipsychotic drugs are not equally effective at suppressing every symptom of these disorders, and thus this has prompted the use of polypharmacy strategies, including multi-target pharmacotherapy.

CME Lesson 15: Psychiatric Disorders and Psychotropic Treatment in the Postpartum Period

____ understood the prevalence and risk factors of psychiatric disorders in the postpartum period.

____ considered the negative effects of psychiatric illness on mothers and infants.

CME Lesson 16: Depression: An Overview and Diagnostic Changes in the DSM-5

____ recalled the high global prevalence of depression with its attendant morbidity.

____ reviewed the various types of depression along with its underlying neurobiology.

CME Lesson 17: From Dementia to Neurocognitive Disorders: DSM-5 Changes

____ summarized changes in the classification of neurocognitive disorders from the *Diagnostic & Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) to the fifth edition of the same manual (DSM-5).

____ appreciated how the new approach offers detailed descriptive and coding opportunities.

CME Lesson 18: Cognitive Impairments in Alcohol-Dependent Subjects

____ reviewed how excessive alcohol consumption induces cognitive impairments mainly affecting executive functions.

____ considered how cognitive impairment can be improved with cessation of alcohol consumption.

CME Lesson 19: Narcolepsy as an Immune-Mediated Disease

____ identified the symptoms of narcolepsy in patients.

____ learned to explain the concept of molecular mimicry and how it may come into play for narcoleptic patients.

CME Lesson 20: Pediatric Pain Assessment and Management: A Systematic Approach Including Psychiatric Assessment

____ considered an evidence-based, systematic approach to pediatric pain management in acute-, chronic-, and palliative-care setting.

____ reviewed widely accepted and potentially adjunctive treatment options while assessing the possible comorbidity of psychiatric illnesses.

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 May 28, 2015,** and the *preliminary* **expiration date is December 31, 2021.** At that point, the Hatherleigh Medical Director and the editorial staff will review the CME material to determine whether the program continues to be consistent with current accreditation guidelines and standards 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 Medicial 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.

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

Directions in Psychiatry is published by The Hatherleigh Company, Ltd., 62545 State Highway 10, Hobart, NY 13788.
POSTMASTER: Please send address changes to: *Directions in Psychiatry*, The Hatherleigh Company, Ltd., 62545 State Highway 10, Hobart, NY 13788.

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Accreditation Standards: IOM; ACGME / ABMS Competencies

Directions in Psychiatry, Vol. 35

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

Institute of Medicine Core Competencies:

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

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

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

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

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

ACGME Competencies:

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

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

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

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

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

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

ABMS Competencies:

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.

Part II-Lifelong Learning and Self-Assessment: Physicians participate in educational and self-assessment programs that meet specialty-specific standards that are set by their member board.

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

Accreditation Standards: IOM; ACGME / ABMS Competencies

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Directions in Psychiatry, Vol. 35 * Part 2					
IOM Core Competencies	**Lesson 6**	**Lesson 7**	**Lesson 8**	**Lesson 9**	**Lesson 10**
Provide patient-centered care	X			X	
Work in interdisciplinary teams					
Employ evidence-base practice	X		X		
Apply quality improvement		X			X
Utilize informatics					
ACGME Competencies					
Patient care	X			X	
Medical knowledge	X		X		X
Practice-based learning and improvement	X				
Interpersonal and communication skills					
Professionalism		X			
System-based practice	X		X	X	X
ABMS MOC Competencies					
Professional standing	X	X			
Commitment to lifelong learning					X
Cognitive expertise	X	X	X		
Performance in practice				X	

Accreditation Standards: IOM; ACGME / ABMS Competencies

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Directions in Psychiatry, Vol. 35 * Part 3					
IOM Core Competencies	**Lesson 11**	**Lesson 12**	**Lesson 13**	**Lesson 14**	**Lesson 15**
Provide patient-centered care		X	X	X	X
Work in interdisciplinary teams				X	
Employ evidence-base practice	X			X	X
Apply quality improvement		X	X		X
Utilize informatics		X	X		X
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		X	X		
ABMS MOC Competencies					
Professional standing	X			X	
Commitment to lifelong learning				X	X
Cognitive expertise	X	X	X	X	X
Performance in practice				X	

Accreditation Standards: IOM; ACGME / ABMS Competencies

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

ABMS Competencies:

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.

Part II-Lifelong Learning and Self-Assessment: Physicians participate in educational and self-assessment programs that meet specialty-specific standards that are set by their member board.

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. 35 * Part 4					
IOM Core Competencies	**Lesson 16**	**Lesson 17**	**Lesson 18**	**Lesson 19**	**Lesson 20**
Provide patient-centered care		X	X	X	X
Work in interdisciplinary teams				X	
Employ evidence-base practice	X			X	X
Apply quality improvement		X	X		X
Utilize informatics		X	X		X
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		X	X		
ABMS MOC Competencies					
Professional standing	X			X	
Commitment to lifelong learning				X	X
Cognitive expertise	X	X	X	X	X
Performance in practice				X	

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Philip Janicak, MD:	Dr. Janicak has received grant/research support from: Janssen, Neuronetics, Inc., Otsuka Pharmaceutical Group; The Research Foundation for Mental Hygiene, Inc.; and has disclosed stock or other financial relationships with Lippencott, Williams & Wilkins.
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Self-assessment Pre-test

for Maintenance of Certification as Required by *The American Board of Psychiatry and Neurology* (ABPN)

This assessment is necessary only for participants using this activity to earn credit hours to satisfy their Maintenance of Certification as required by *The American Board of Psychiatry and Neurology* (ABPN).

Please answer and review each self-assessment question before starting your CME program.
This self-assessment will *not* be scored by Hatherleigh.

Directions in Psychiatry, Vol. 35

1. **Studies indicate that individuals who use cannabis have a higher risk of developing a psychotic disorder than individuals who do not.**
   A. This statement is true.
   B. This statement is false.

2. **Randomized controlled trials can be easily used to evaluate the effectiveness of various psychotherapeutic treatments.**
   A. This statement is true.
   B. This statement is false.

3. **Women use mental health services more frequently than men.**
   A. This statement is true.
   B. This statement is false.

4. **Criteria for bipolar disorder in the DSM-IV-TR are the same as criteria in the DSM-5.**
   A. This statement is true.
   B. This statement is false.

5. **Which one of the following medications is approved by the FDA for the treatment of bipolar disorder in children who are 10 years of age and older?**
   A. Lithium
   B. Carbamazepine
   C. Risperidone
   D. All of the above

6. **Peter Lewinsohn, who was influenced by B.F. Skinner's work, is considered the father of behavioral activation. Lewinsohn postulated that:**
   A. Depressed individuals experience increased aversive events and decreased pleasant events.
   B. Cognitive restructuring is key to help patients engage in behavioral activation strategies.
   C. Increased frequency of punishment was a basis of depression.
   D. All of the above

7. **What is the name of the procedure when a patient is asked to imagine the steps involved and possible obstacles that could arise when executing a given task?**
   A. Task planning
   B. Cognitive rehearsal
   C. Imagery rescripting
   D. Guided discovery

8. ***Chronic obstructive pulmonary disease* (COPD) is found to be the _____ leading cause of death in the United States after heart disease, cancer, and stroke.**
   A. First
   B. Second

C. Third
D. Fourth

9. Which of the following is correct regarding cognitive impairments in COPD and *obstructive sleep apnea syndrome* (OSAS) patients?

A. Low *forced expiratory volume* (FEV_1) during middle age is found to be a significant predictor of cognitive disabilities in later life.
B. Low oxygen desaturation is related to impaired cognitive functions.
C. Hypoxemia is present in both COPD and OSAS and is responsible for the majority of cognitive impairments in patients.
D. All of the above

10. Self-agency in narcissistic personality disorder is affected by all of the following, *except*:

A. Unstable or incoherent goals
B. Perfectionism and high aspirations
C. Impulsivity
D. None of the above

11. What are the subtypes of Internet addiction?

A. Excessive gaming or gambling
B. Sexual preoccupations (cybersex)
C. Socializing/social networking
D. All of the above

12. Insomnia often:

A. resolves itself without treatment.
B. resolves itself after treatment of a comorbid condition.
C. exacerbates medical conditions.
D. does not cause functional impairment.

13. Which of the following statements is true regarding insomnia and comorbid medical conditions?

A. When depression is treated in patients with insomnia, sleep disturbances and fatigue are often restored.
B. Chronic insomnia, if left untreated, can exacerbate mood problems and increase suicidal behaviors.
C. When insomnia is clearly precipitated by another medical condition, the insomnia resolves itself when the medical condition is treated.
D. Sleep disturbance is a minor symptom of major depressive disorder.

14. Which of the following is a commonly overlooked aspect of predisposing psychopathologies associated with posttraumatic stress disorder?

A. Personality disorders
B. Conduct disorder
C. Depression
D. All of the above

15. Which of the following is *not* among the disorders found to arise from disaster-related trauma in patients:

A. Panic disorder
B. Schizophrenia
C. Generalized anxiety disorder
D. Major depressive disorder

16. Retraumatization in patients can lead to:

A. clinician burnout.
B. staff attrition.
C. both A and B.
D. none of the above.

17. **There are three commonly used terms describing drug co-administration which include all of the following, *except*:**
    A. Combination
    B. Augmentation
    C. Decreasing
    D. All of the above

18. **All of the following are ideal pharmacokinetic characteristics for a medication suitable for lactation, *except*:**
    A. a short half-life.
    B. low maternal protein binding.
    C. a low milk-to-plasma ratio.
    D. low lipid solubility.

19. **All of the following features would be present in a 22-year-old woman with premenstrual dysphoric disorder, *except*:**
    A. affective lability, anger, irritability.
    B. symptom onset in the final week before menses.
    C. symptoms start to abate with the onset of menses.
    D. mood-congruent auditory hallucinations.

20. **Alcohol-dependent patients who become abstinent achieve improvement of cognitive functioning after a period of several months.**
    A. This statement is true.
    B. This statement is false

21. **Risk factors associated with chronic alcohol consumption include:**
    A. Comorbid psychiatric disorders.
    B. Early-life stress exposure
    C. Impulsivity
    D. All of the above.

22. **Narcoleptic patients typically have lower levels of:**
    A. vitamin D levels.
    B. hypocretin *cerebrospinal fluid* (CSF) levels.
    C. oxygen in their blood.
    D. sodium in their urine.

23. **In the case of treating pain in children with sickle-cell disease in crisis, an opioid medication like morphine is considered an appropriate first-line medication; and increasing the dosage is warranted for acute flare-ups.**
    A. This statement is true.
    B. This statement is false.

24. **The key components of optimal childhood pain management include all of the following, *except*:**
    A. the use of patient pain-assessment tools providers should create to reflect their patient panels.
    B. the provision of anticipatory guidance about pain and its recurrence.
    C. the prescription of pain medications commensurate with each patient's measured pain level.
    D. the administration of regular assessments that use validated tools to screen for depression and anxiety.

25. **Barriers to pain management include all of the following, *except*:**
    A. the lack of clarity regarding who should be a child's primary pain manager.
    B. multidisciplinary, pediatric pain-rehabilitation centers' exclusion of children from receiving pain-management treatment unless they have life-limiting conditions.
    C. parents' and providers' concerns that children might overdose.
    D. the persistent lack of anticipatory guidance for predictable pain recurrences, such as post-operative pain in children with recurrent illnesses.

This is the end of your self-assessment test for volume 35
This self-test is for your reference only. Please do not submit these answers to Hatherleigh.

Self-Assessment Answer Key

1.A. 2.B. 3.A. 4.B. 5.C. 6.D. 7.B. 8.D. 9.D. 10.C. 11.D. 12.C. 13.B. 14.A. 15.B. 16.C. 17.C. 18.B. 19.D. 20.A. 21.D. 22.B. 23.A. 24.A. 25.C

Directions in Psychiatry

Breakdown of Tested Areas for Volume 35

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

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

Topic Areas/ Lesson numbers & possible questions correct.		Topic Areas/ Lesson numbers & possible questions correct.	
Addictions: **Lessons:** 9, 10, 12, 18	x/16	**Mood Disorders:** **Lessons:** 3, 4, 5, 6, 9, 10, 16	x/28
Anxiety Disorders: **Lessons:** 10	x/4	**Neurobiology:** **Lessons:** 1, 8, 16, 17	x/16
Child/Pediatric, Adolescent Psychiatry: **Lessons:** 4, 5, 20	x/12	**Pain/Palliative Care:** **Lesson:** 20	x/4
Cognitive Disorders: **Lesson:** 17, 18	x/8	**Personality Disorders:** **Lessons:** 9	x/4
Cultural Psychiatry: **Lesson:** NA	x/0	**Professional Standards:** **Lessons:** 2, 7	x/8
Developmental Disorders: **Lessons:** NA	x/0	**Psychopharmacology:** **Lessons:** 4, 5, 11, 12, 14, 15, 20	x/28
Dissociative Disorders: **Lessons:** NA	x/0	**Psychotic Disorders:** **Lessons:** 1, 3, 14	x/12
Domestic Violence: **Lessons:** NA	x/0	**Psychosocial Treatment / Psychotherapy** **Lessons:** 1, 2, 4, 5, 6, 11, 18, 20	x/32
Eating Disorders: **Lessons:** NA	x/0	**PTSD/Trauma/Disaster Psychiatry:** **Lessons:** 12, 13	x/8
Ethical Issues: **Lesson:** 7	x/4	**Sexual Disorders: Gender, Paraphilia, Dysfunction:** **Lessons:** NA	x/0
Family Psychiatry: **Lesson:** 4, 5	x/8	**Sleep Disorders:** **Lesson:** 8, 11, 19	x/12
Geriatrics: **Lessons:** NA	x/0	**Somatoform Disorders:** **Lessons:** NA	x/0
HIV/AIDS/Infectious Disease: **Lessons:** NA	x/0	**Suicide & Suicide Prevention:** **Lessons:** 9	x/4
Impulse Control Disorders: **Lesson:** NA	x/0	**Technology in Psychiatry:** **Lesson:** NA	x/0
Malpractice Risk/Forensics: **Lessons:** NA	x/0	**Women's Issues:** **Lesson:** 3, 13, 15	x/12
Medical Errors: **Lessons:** NA	x/0	**Other Clinical Issues:** **Lessons:** 1, 8, 19	x/12

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Neurodevelopmental and Environmental Hypotheses of Negative Symptoms of Schizophrenia

Frédéric Limosin, MD, PhD

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

KEY WORDS: Schizophrenia • Negative symptoms • Environment • Neurodevelopmental hypothesis

LEARNING OBJECTIVES: This lesson examines the role of environmental factors which are often implicated in the course of schizophrenia in adults. Readers will consider how certain psychosocial and biological factors have shown an increased risk of them developing schizophrenia.

LESSON ABSTRACT: The negative symptoms of schizophrenia, avolition, alogia, apathy and impaired or nonexistent social functioning, are strongly correlated with the progressive course and long-term prognosis of the disease, undermining the patient's ability to integrate socially, interpersonal skills and quality of life. At a time when new drug strategies are being developed, a better understanding of the etiology and pathogenesis underpinning the occurrence of negative symptoms constitutes an essential prerequisite for real therapeutic advances. Approaching this vulnerability from the neurodevelopmental perspective is especially pertinent with regard to the experimental studies conducted in animals. Several models have been put forward, involving a variety of topics such as the deleterious impact of a prenatal infection or of early maternal deprivation on brain development, or else the consequences of trauma and abuse suffered during childhood. These various models are based on biological abnormalities that could guide the identification of new therapeutic targets. They notably include the hyperreactivity of the hypothalamic-pituitaryadrenal axis and dysfunction of corticostriatal glutamatergic transmission. As such, in the traumagenic model, which associates neurodevelopmental and neurodegenerative processes, the dysfunction of corticostriatal glutamatergic transmission, by reducing the tonic dopamine release, could be the cause of an increase in the phasic dopamine release linked to stress. This excessive phasic response to stress may induce cerebral damage by increasing excitotoxicity and oxidative stress.

COMPETENCY AREAS: This lesson presents a brief overview of models which examine the correlation of environmental factors in the course of schizophrenia. Readers will gain knowledge concerning psychosocial factors such as, but not limited to: immigration, environment, early parental/child relationships, toxicity factors, and the role of infectious agents that may contribute to the etiology of symptoms in schizophrenia.

Introduction

The complexity and clinical heterogeneity of schizophrenia raise questions about the respective roles of the various vulnerability factors involved. Among these factors, those related to the environment, whether of a psychosocial or biological nature, whether occurring early or later, remain non-specific factors that may play a role in the etiology and course of the disorder.

The neurodevelopmental hypothesis is founded on evidence from clinical, experimental and brain imaging findings. This model is based on the occurrence of early abnormalities in neurodevelopmental processes, well in advance of the onset of the disorder. The main neurodevelopmental hypotheses implicate structural abnormalities involving the migration of neurons and laminar differentiation of the cortex, occurring during the second trimester of pregnancy. However, all stages of normal brain development may be involved, from the proliferation of stem cells to the differentiation and migration processes, and then from dendritic and axonal growth to the myelination process, a process that continues at least until early adulthood, notably in the prefrontal cortex.

Review

Epidemiological studies of separation/adoption, of half-siblings and twins show that the familial clustering of cases of schizophrenia is not solely the result of genetic factors, but also of environmental factors. Twin studies estimate heritability at approximately 80%,[1] while Lichtenstein et al., in a register-based study of Swedish families, determined that the genetic factors accounted for 64% of the vulnerability to develop schizophrenia, compared to 36% for environmental factors.[2] Even if the respective influence of these two types of vulnerability factors varies according to the disease subtype (hence the importance of distinguishing disease phenotypes), their interaction appears to be fundamental to the etiology and course of the disorder. In addition, the notion of vulnerability and the role of environmental factors are complex notions in more than one respect:

1. **Firstly, the influence of environmental factors can be exerted on the occurrence of the disorder, by contributing to the underlying etiology, as well as on its progressive course, whether this be in terms of clinical characteristics (severity, age of onset, comorbidities, etc.), or in terms of the response to drug treatments.**

2. **Secondly, the notion of environment encompasses highly varied factors, both by their nature (demographic, climate, dietary, psychological, etc.) and by the stage of development at which they intervene. As such, 'early' environmental factors, whose influence is exerted well in advance of the onset of the disease, such as pre-and perinatal factors, are distinguished from 'late' factors, such as, for example, the role of stressful life events in the progressive course of the disorder. Ultimately, the environment is understood in a very broad, and thus heterogeneous sense, ranging from the internal biological environment to the external context.**

3. **Lastly, we can no longer consider environmental factors in isolation but rather must consider them within integrated vulnerability models. In addition, more so than causal risk factors, vulnerability factors are considered to be predisposing disease factors or intermediate factors whose influence alone would be insufficient to trigger the onset of the disorder. In these models, the interactions between environmental factors and genetic factors appear to be especially relevant.**

Environmental Factors Most Often Implicated

Psychosocial Factors:

- **The consequences of *immigration* have given rise to several epidemiological studies, notably in England and the Netherlands, which found an increased risk of developing schizophrenia in immigrants, whether of the first or second generation.[3] This risk**

could be partly due to conditions of greater social adversity, but other hypotheses have been put forward, such as the mother's diminished immunity to the viruses of the host country.

- **The psychological effect of an urban environment may also interact with levels of reality distortion and depressive symptoms in people experiencing first-episode psychosis and may affect the syndromal presentation of psychotic disorders.[4] For individuals suffering from psychosis, spending time in an urban environment makes them think more negatively about other people and increases their paranoia.[5]**
- **The role of disturbances in early parent/child relationships, whether it be early separation, a lack of emotional support and physical contact, or abuse, has also been invoked in the later development of the disorder. Zugno et al. showed that rats subjected to maternal deprivation had an increased risk for schizophrenia-like behavior and cholinergic alteration.[6]**

Biological Factors:

- ***Toxicity factors*, foremost among them, psychoactive substances like cannabis, amphetamines or cocaine, can cause acute episodes punctuating the course of the disorder. In most cases, the toxic agents involved determine to a lesser extent the onset of a chronic disease than they precipitate its onset or interfere with its progressive course, making it worse with more complications and sometimes poorer treatment response.[7] Nonetheless several prospective cohort studies on the general population have shown that subjects who use cannabis had a higher risk of developing a psychotic disorder.[8]**
- ***Role of certain infectious agents:* It was during the nineteenth century that the hypothesis of the role of infectious agents in the occurrence of schizophrenia, as well as in bipolar disorder, was first formulated, notably by Jean Esquirol in 1845, followed by Eugen Bleuler in 1911 and Emil Kraepelin in 1919.[9] This hypothesis was in line with the discovery of the infectious nature of the psychiatric manifestations of syphilis which occurred during the eighteenth century. Among the different infectious agents, the influenza virus has been implicated most often. Its pathogenic role was suggested for the first time during the 1918 pandemic: many individuals who contracted the "Spanish: flu developed psychiatric disorders, especially with clinical presentations that resembled schizophrenia, as described at the time by Menninger.[10]**

However, the epidemiological starting point for the hypotheses formulated on the role of early environmental vulnerability factors was the demonstration of a seasonal imbalance in the distribution of births of future patients, which is evident in schizophrenia. **Many studies have identified, in the Northern Hemisphere, an excess of births of subjects with schizophrenia during the winter and early spring, especially between December and April.[11] On average, it is estimated that in European and North American countries, the proportion of subjects with schizophrenia born in winter or at the start of spring exceeds the figures expected in the general population by about 5 to 15%.** The "age-incidence" effect, which concerns all diseases where the incidence increases with the age of subjects, seems too small to account for the observed seasonal peak of births. In addition, the existence of this peak during the austral winter in the Southern Hemisphere, even though it is less evident, runs counter to such a bias.[12] This phenomenon of seasonal imbalance is not specific to schizophrenia, since it is found in other diseases like bipolar disorder[13] or substance or alcohol abuse.[14]

In order to account for the observed seasonal distribution of births, various hypotheses have been put forward, some of which are more satisfactory than others: climate, dietary, obstetrical, chronobiological or infectious. Among these alternatives, two quickly gained

traction: the role of obstetrical complications and the infectious hypothesis, falling in line with a neurodevelopmental model of schizophrenia.

- ***Role of obstetrical complications:*** **obstetrical complications are associated with an increased risk of developing schizophrenia. It is a well-documented yet low risk with an odds ratios adjusted for the effect of exposure being approximately 2. The complications most often involved are bleeding during pregnancy, pre-eclampsia and gestational diabetes, as well as certain delivery complications, such as uterine atony, neonatal asphyxia and hemorrhage.[15] Once again, this association is not specific to schizophrenia, as a higher frequency of obstetrical complications has been found in other psychiatric disorders, such as mood disorders, anorexia nervosa or autism.[16,17]**

- ***Role of the influenza virus:*** **influenza infection during the gestation period is associated with an increased risk for the child of later developing schizophrenia.[18] Once again, this association is not specific to this diagnosis, as it is found, for example, in the predisposition to unipolar mood disorder.[19] The mechanism of action of the influenza virus has not been elucidated, but the leading hypothesis suggests that in certain genetically predisposed mothers, antiviral maternal antibodies could cause an autoimmune reaction which is harmful to the fetal brain.[20]**

The Neurodevelopmental Hypothesis Applied to Negative Symptoms

The negative symptoms of schizophrenia include avolition, alogia, apathy and impaired or nonexistent social functioning. The negative symptoms are so called because they are an absence as much as a presence: inexpressive faces, monotone and monosyllabic speech, few gestures, seeming lack of interest in the world and other people, inability to feel pleasure or act spontaneously. Origin of the definition of the negative symptoms can be found in the work of John Hughlings Jackson.[21] From 1874 to 1876, Hughlings Jackson adapted Herbert Spencer's evolutionary theory to neurological disease and addressed the relationship between the centres in his hierarchy. Following Spencer, Hughlings Jackson concluded that the highest nervous centres evolved out of the lower. Patients with diseases of the highest centres develop two types of symptoms, negative symptoms due to the loss of higher centres and positive symptoms due to the emergence of lower centres. Positive symptoms are simpler and less differentiated than the negative symptoms which they replace.[21] Furthermore, recent data suggest that negative symptoms should not be considered only as a unitary construct, and that measurement of these symptoms should distinctly assess motivation, pleasure, and emotion expression factors.[22] Moreover, particular attention should be paid to the distinction between primary versus secondary negative symptoms and between prominent and predominant negative symptom profiles.[23]

The frequency of the deficit syndrome varies depending on the progressive stage of the disease, from about 15% for the first episodes up to 25-30% for the later phases.[24] The wider use of second-generation antipsychotics may have permitted an appreciable reduction in the prevalence of negative symptoms; at least, this is what the recent study by Shivashankar et al.[25] suggests, finding such a reduction over a period of 25 years (between 1981 and 2006). The fact nevertheless remains that negative symptoms comprise a major factor in interpersonal and social isolation and impairment of quality of life. Yet, even if negative symptoms are associated with greater genetic determinism than positive symptoms,[26-29] the analysis of the neurodevelopmental factors likely to be involved in their occurrence appears to be relevant in more than one respect, especially from the perspective of identifying new therapeutic targets.

Data from Epidemiological Studies

Several studies have demonstrated an association between prenatal infection and certain functions and morphological brain abnormalities in patients with schizophrenia, whether they be in executive function

deficits or an enlarged cavum septum pellucidum, suggestive of dysgenesis.[30,31]

Some studies have found an association between the peak of birth seasonality and certain clinical forms, mainly disorganized subtype,[32] paranoid subtype[33] or with pronounced negative symptomatology.[34] In addition, patients with schizophrenia who were exposed to an elevated risk of influenza infection during pregnancy are more likely to be single, which could indicate poorer social adjustment,[35] and with the disorganized clinical subtype.[18]

Experimental Studies Conducted in Animals

Prenatal Infection Model:

One of the experimental models used to analyze the impact of a prenatal infection consists of injecting the pregnant female rodent with polyriboinosinic-polyribocytidylic acid (Poly I:C), a synthetic analog of double-stranded RNA that stimulates an immune response with cytokine secretion. It has been shown that this exposure is the cause of cognitive, behavioral and pharmacological dysfunction in the neonate as an adult, and that these abnormalities result in disorders found in schizophrenia, such as disorders of sensorimotor gating, selective attention, working memory or hypersensitivity to psychostimulants.

In addition, the timing of this exposure appears to be paramount, since the abnormalities induced will vary, depending on the stage of pregnancy. Thus, if exposure is late, at the end of gestation, one observes as an adult rodent persistent behavioral abnormalities with learning disabilities,[36] disturbance of visual-spatial working memory[37] and hypersensitivity to the glutamatergic *NMDA* (N-methyl-D-aspartate) receptor blockade during treatment with the antagonist *dizocilpine* (MK-801).[37] They thus involve precisely the dysfunctions that may underpin the negative symptoms found in schizophrenia.

Bitanihirwe et al.[38] injected mice with Poly I:C on gestation day 17, hence during the late gestational phase. In those neonates grown as adults, deficits in social interaction, anhedonic behavior, and alterations in locomotor behavioral response to acute administration of *apomorphine* (Apokyn) were demonstrated. In addition, male subjects were found to lack cognitive and behavioral flexibility. Lastly, the authors found reduced levels of dopamine and glutamate in the *prefrontal cortex* (PFC) and hippocampus, as well as decreased levels of γ-*aminobutyric acid* (GABA) in the hippocampus and of glycine in the PFC. These abnormalities are in favor of a neurodevelopmental model that could account for the occurrence of negative symptoms, with, in addition, an effect correlated with gender.

Experience of Maternal Deprivation:

In the neonate rat, long periods of maternal deprivation (from 3 to 24 hours versus 3 to 15 minutes) are associated with hyperactivity of the *HPA* (hypothalamic-pituitary-adrenal) axis,[39,40] and with a *prepulse inhibition* (PPI) deficit or lack of reduction in the intensity of startle.[41] The term PPI describes the inhibition of the startle reflex triggered by a violent and unexpected exteroceptive stimulus (pulse) when it is preceded in the short term by a weaker prestimulus (prepulse), too weak to itself induce the reflex. PPI is thus an operational measure of sensorimotor gating, reflecting the capacities of the individual to regulate, to "buffer" the input of different levels of significance and variable chaotic flow of sensory information. Maternal deprivation is also accompanied by cognitive disorders with impaired learning abilities.[42,43]

Moreover, there is a period of brain development particularly sensitive to the deleterious effects of maternal deprivation: the stress hyporesponsive period, which falls, for the rat, between the 4th and 14th postnatal day. Takase et al.[44] thus showed that among rats subjected to maternal deprivation during this critical period, only the postpubertal males had abnormal hippocampal calcineurin expression associated with a deficit in social interactions and objective memory. Once again, this is an animal model linking negative symptoms and neurodevelopmental impairment.

The Traumagenic Neurodevelopmental Model

This model was proposed in light of two observations: that of the high prevalence of childhood abuse in patients with schizophrenia,[45] and that of the similarities between the effects on brain development of the trauma

from abuse and certain biological abnormalities found in patients with schizophrenia, whether it be hyperreactivity of the HPA axis or morphological changes to the brain (cerebral atrophy, ventricular enlargement, reversed cerebral asymmetry, hippocampal lesions).

Ross et al.[46] showed that a history of abuse was negatively correlated with negative symptoms. However, there may be two distinct patterns of response to stress:

- **Some subjects repeatedly confronted with abuse react through dissociative and positive symptoms: it then involves not so much a process of cerebral atrophy, as dysfunction mediated by dopamine, whence a better response to antidopaminergics.[47]**
- **Other subjects react through hypervigilance (anxiety, hypersensitivity) that may accentuate the phenomenon known as "pruning," normally occurring at adolescence and corresponding to a decrease in the number of synapses (especially in the neuropil) and to neuronal loss. This excessive neuronal loss could be at the root of the progression toward negative symptoms in adulthood.[47,49]**

In this latter model, which associates neurodevelopmental and neurodegenerative processes, the glutamate hypothesis could also play a role. In fact, dysfunction of corticostriatal glutamatergic transmission, by reducing the tonic dopamine release, could be the cause of an increase in the phasic dopamine release linked to stress. This excessive phasic response to stress may induce cerebral damage by increasing excitotoxicity and oxidative stress.

Lastly, still in this mixed model associating a neurodevelopmental approach and a neurodegenerative process, some immune dysfunction could be involved, mainly implicating the role of pro-inflammatory cytokines.[50]

Conclusion

The negative symptoms of schizophrenia are a major factor in interpersonal and social isolation and the impairment of quality of life, and thus represent a major issue in the field of development of new therapeutic strategies, notably drug strategies. As such, a better understanding of the pathogenic mechanisms that underpin the occurrence of negative symptoms is an essential prerequisite for the identification of therapeutic targets. In this perspective, the neurodevelopmental approach appears particularly relevant, especially with regard to experimental animal studies, which have made it possible to demonstrate a number of biological abnormalities. These notably include hyperreactivity of the HPA axis and dysfunction of corticostriatal glutamatergic transmission. Additionally, given the modest impact of drug treatments for negative symptoms to date,[51] psychological factors associated with the development of these symptoms are of considerable importance and may be viable treatment targets.[52]

About the Faculty

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

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L903343

Multiple-Choice Questions

1. In the Northern Hemisphere, being born during which seasons is associated with an increased possibility of a schizophrenia diagnosis:

A. Winter and early spring

B. Summer

C. Fall and early winter

D Late autumn and late winter

2. All of the following are negative symptoms of schizophrenia, *except*:

A. Alogia

B. Avolition

C. Excessive spontaneous behavior

D. Inability to feel pleasure

3. For individuals suffering from psychosis, spending time in an urban setting:

A. leads to increased exposure to air pollution, which decreases brain function.

B. makes individuals think more negatively about others and increases their paranoia.

C. results in greater exposure to mental health resources and is associated with positive treatment outcomes.

D. is correlated with increased rates of long-term hospitalization.

4. According to the lesson, prenatal exposure to which illness is correlated with an increased schizophrenia diagnosis in adulthood?

A. The common cold

B. Chicken pox

C. Measles

D. Influenza

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Best Practices in CME

Neurodevelopmental and Environmental Hypotheses of Negative Symptoms of Schizophrenia

By Frédéric Limosin, MD, PhD

ID#: L903343

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

CME Lesson Overview

This lesson examines the correlation of environmental factors in the course of schizophrenia. Readers will gain knowledge concerning psychosocial factors such as, but not limited to: immigration, environment, early parental/child relationships, toxicity factors, and the role of infectious agents that may contribute to the etiology of symptoms in schizophrenia.

Key Point 1: Overview

Epidemiological studies indicate that familial clustering of cases of schizophrenia is not solely the result of genetic factors, but also environmental factors.

Key Point 2: Understanding of Environment

The environment includes varied factors ranging from the internal biological environment to the external context throughout the course of schizophrenia; these factors include demographic, climate, dietary, psychological, etc. Genetics coupled with environmental factors in schizophrenia when reviewed in the context of vulnerability factors that may be predisposing disease factors.

Key Point 3: Implications of Environmental Factors

Studies examining consequences of immigration, the psychological effect of an urban environment, and the role of disturbance in early parent/child relationships demonstrated an increased risk in individuals developing schizophrenia.

Key Point 4: Implications of Biological Factors

Studies indicate that individuals affected by toxicity factors, particularly psychoactive substances, have a higher risk of developing a psychotic disorder. Further, certain infectious agents such as the influenza virus has been implicated in the course of psychiatric disorders.

Key Point 5: Neurodevelopmental Models

Neurodevelopmental models observed that there is a higher prevalence of childhood abuse in patients with schizophrenia. Understanding research that explores the impact of prenatal infection or early maternal deprivation on brain development could help identify new therapeutic strategies.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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The Place of Psychotherapy in Contemporary Psychiatry

Saman Tavakoli, MD

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

KEY WORDS: Psychotherapy • Psychiatry • ACGME Training

LEARNING OBJECTIVES: Upon completion of this lesson, clinicians will recognize that psychotherapy is still a very relevant part of clinical psychiatry. Clinicians will consider the necessity to develop evaluation methods to measure the effectiveness of psychotherapy.

LESSON ABSTRACT: Psychotherapy has long been an essential component of clinical psychiatry and many young physicians choose to train in psychiatry residency programs in order to acquire necessary knowledge and skills, and become competent psychotherapists. Recent advances in psychopharmacology and neuroscience, and growing dominance of managed care and evidence-based medicine have had dramatic impacts on health care delivery systems and clinical psychiatry practice. Despite these changes in the field of mental health, psychotherapy still remains a crucial part of clinical psychiatry and comprises a great proportion of psychiatrists' clinical practice. Hence, accreditation agencies and regulatory bodies determine compulsory minimum requirements for psychiatry residency programs to ensure that residents, at the end of their specialty training, can demonstrate competence in managing their patients through applying different approaches of psychotherapy.

COMPETENCY AREAS: This lesson informs clinicians of the need and necessity of psychotherapy in clinical psychiatric practice.

Introduction

Psychotherapy has long been an essential component of clinical psychiatry and many young physicians choose to train in psychiatry residency programs in order to acquire necessary knowledge and skills, and become competent psychotherapists. Recent advances in psychopharmacology and neuroscience, and growing dominance of managed care and evidence-based medicine have had dramatic impacts on health care delivery systems and clinical psychiatry practice. **Despite these changes in the field of mental health, psychotherapy still remains a crucial part of clinical psychiatry and comprises a great proportion of psychiatrists' clinical practice.** Hence, accreditation agencies and regulatory bodies determine compulsory minimum requirements for psychiatry residency programs to ensure that residents, at the end of their specialty training, can demonstrate competence in managing their patients through applying different approaches of psychotherapy.

At the turn of the 20th century, Sigmund Freud, an eminent Austrian neurologist, developed psychoanalysis as "a procedure for the investigation of mental processes", "a method for the treatment of neurotic disorders", and "a collection of psychological information obtained along those lines."[1] During the first half of the century, psychoanalysis became the dominant paradigm in psychiatry and the main approach for the treatment of psychiatric disorders. Following the introduction of psychiatric medications in the next decades, however, the situation changed. In less than a decade after the identification of lithium's sedative effects and its efficacy in the treatment of manic patients by John Cade in 1949, prototype drugs for other mental conditions were also discovered. Chlorpromazine (an antipsychotic), iproniazid (a monoamine oxidase inhibitor), imipramine (Tofranil; a tricyclic antidepressant), and chlordiazepoxide (Librium; a benzodiazepine) were all identified within less than 10 years. Pharmacological treatments for major psychotic, mood, and anxiety disorders were developed by the end of the 1950s.[2] The achievements gained during 1945-1957 not only revolutionized the biological treatment of psychiatric disorders, but also attracted attention to the role of neurotransmitters in the etiology of such disorders. Subsequent to the mentioned achievements, efforts were made, particularly during the second half of the 20th century, to develop biological models to explain psychiatric disorders and to propose novel psychiatric medications. In other words, psychiatry, which used to endorse 'soft' bases of interpersonal relationships, shifted toward a 'hard' scientific approach in which physicochemical models were expected to explain psychiatric disorders. The 'hard' scientific approach assumes that such models can simply be assessed through scientific and empirical methods and are thus more reliable than models using 'soft' bases. It also argues that applied physics and chemistry can ultimately resolve all problems in the world, including psychiatric disorders.[3] Therefore, in order to consider a body of knowledge as scientific and reliable or to administer a particular treatment modality for psychiatric disorders, rigorous methodologies have to be applied to validate that knowledge or determine the efficacy of those treatment methods. In this context, understanding the position of psychotherapy in contemporary psychiatry would be more complex. In efforts to resolve the problem of empirical support for psychotherapies, evidence has been provided by the application of acceptable methodologies in numerous studies on the efficacy of some short-term manualized therapies, e.g. cognitive-behavioral therapy, in the treatment of various psychiatric disorders. **Nevertheless, common research methods in medicine and *randomized controlled trials* (RCTs), as the 'gold standard' of evidence, cannot be easily used to evaluate psychotherapies, particularly long-term psychodynamic psychotherapy, or those dealing with a wide range of symptoms and problems (e.g. personality disorders).** Some scholars, however, contend that research to evaluate the efficacy of psychotherapeutic methods is more challenging and complex, but essentially not less possible, than that in other fields of medicine. Methodological complexities, the required time and cost for such research, and pharmaceutical companies' refusal to invest in psychotherapeutic research limit the number of studies on the efficacy of psychotherapies, particularly long-term and dynamic psychotherapies.[4,5] Some believe that for psychotherapy, as a psychiatric practice, to survive under the dominance of evidence-based medicine, researchers should insist on the inapplicability of common efficacy

evaluation methods and RCTs to psychotherapy, and also define appropriate criteria and methods to assess the usefulness of psychotherapies.[6]

Despite the development of various medications and drug classes over the recent decades, the new drugs do not seem to be more effective than their ancestors. In fact, none of the novel antidepressants can supersede the first generation of antidepressants (such as imipramine and monoamine oxidase inhibitors) introduced in the 1950s. Consequently, many patients gain modest benefits or none at all. Likewise, the antipsychotic efficacy of clozapine (discovered in 1960) has not been surpassed by any new drugs. Although numerous mood-stabilizing drug classes have been introduced during the past years, lithium is still the standard treatment for bipolar disorder.[2] Meanwhile, there is no pharmacological treatment with documented efficacy for the core symptoms and psychopathology of some disorders such as social and language deficits in autism, negative symptoms of schizophrenia, and core psychopathological elements of personality disorders. **In other words, despite the advances in psychopharmacology, the role of psychotherapy in understanding the etiology and treatment of psychiatric disorders cannot be neglected.** Moreover, it is recommended in various clinical practice guidelines for most psychiatric disorders as a single treatment or in combination with other therapeutic modalities.[7]

In their introduction to the *American Psychiatric Publishing Textbook of Clinical Psychiatry*, Gabbard et al. write about a dichotomy due to the existence of conflicting views in psychiatry.[5] Based on this dichotomous perspective, while psychotherapy was applied for problems with psychological origins, disorders and conditions originating from the human brain were to be treated with biological and pharmacological treatments.[8] However, based on later studies, especially those performed by Eric Kandel, psychotherapies act at the synaptic level in the brain and psychotherapeutic process could be described as an environmental experience influencing gene expression in patients.[8] In other words, similar to pharmacological treatments, psychotherapies tend to help patients by affecting the brain. According to Lipowski, "after a period of 'brainless' psychiatry during which the focus was merely on psychodynamic and social factors, the attention was shifted toward contrasting ideas such as radical biologism and 'mindless' psychiatry."[9] **These dichotomous perspectives are currently supplanted by a more balanced view which considers psychotherapy as a basic science—like biochemistry and anatomy—applicable to all fields of psychiatry.[9] Furthermore, psychotherapy can be defined as a biological treatment that helps patients by causing particular changes in their brain.**

Psychotherapy in Psychiatric Practice:

Despite the remarkable progress in the development and application of pharmacological treatments for psychiatric disorders, psychotherapy is still playing a critical role in the treatment of psychiatric patients. **While about 3% of Americans receive psychotherapy from their psychiatrists, psychologists, and social workers per annum,[10] psychiatrists have a unique place in the treatment of psychiatric patients, as they are the only group of mental healthcare providers capable of prescribing medicines and providing integrative pharmacotherapy and psychotherapy.** Since combining medication prescription with psychotherapy is a major characteristic of current psychiatric practice, competency in conducting such care is a key component of the required training for psychiatrists. Surveys conducted in countries such as the USA and Canada show that psychiatrists spend a substantial amount of their clinical practice providing psychotherapy.[11] Olfson et al. found that "psychotherapy was received by 79% of the patients visiting psychiatrists."[11] Similarly, a previous study reported that 92% of psychiatrists spend about half of their time in clinical practice performing psychotherapy.[11] Following recent changes in reimbursement policies and the insurance companies' willingness to cover brief medication management visits, particularly in the USA, researchers have increasingly focused on trends of psychotherapy practice by psychiatrists. Mojtabai and Olfson evaluated the national trends in psychotherapy provision by psychiatrists in their offices in the USA. They reported a decline in the visits involving psychotherapy by psychiatrists, from 44.4% in 1996-1997 to 28.9% in 2004-2005.[7]

In other words, although psychotherapy occupies a great proportion of psychiatrists' time, the

availability of psychiatric medications with few side effects, managed care, reimbursement policies, and the insurance companies' inclination to cover brief Med Checks have all contributed to the reduction in psychotherapy provision by psychiatrists in recent years.[7] Furthermore, the growing number of patients with mental health care demands along with the limited number of psychiatrists results in long waiting lists. Financial factors are also partly responsible for the observed trend. In fact, psychiatrists earn substantially greater income from brief Med Checks than from psychotherapy. For instance, in the USA, over a 45-50-minute period, a psychiatrist can manage three 15-minute brief medication management visits and earn $150. However, devoting the same time to psychotherapy would yield $90.7.[7] Studies show that patients who paid treatment costs out of pocket had the highest chance of receiving psychotherapy. Moreover, patients with private insurance were more likely to receive psychotherapy than those covered by public insurance.[7] One interesting finding was that over 40% of psychiatrists provided psychotherapy for either all or none of their patients. This finding suggests an ideological dichotomy in contemporary psychiatry, i.e. a large group of psychiatrists belong to one of the psychotherapy or the pharmacotherapy camps.[7]

Based on surveys on psychiatric practice, one can conclude that despite the recent reduction in psychotherapy provision by psychiatrists, this method of care is still a major part of clinical psychiatry. Developing competency in psychotherapy provision should thus be regarded as an indispensable component of psychiatric training.

Psychotherapy in Psychiatric Training:

As discussed earlier, psychotherapy is a defining characteristic of psychiatrists' career.[4] **Surveys have demonstrated that psychiatrists devote a considerable proportion of their clinical practice time to psychotherapy.**[11] On the other hand, acquiring the knowledge and skills required for psychotherapy is one of the major reasons young physicians choose to study psychiatry.[12] In a study by Hadjipavlou and Ogrodniczuk, a large proportion of psychiatry residents reported the chance to learn and practice psychotherapy as an important factor for selecting psychiatry as their future career. Moreover, they introduced their competency in psychotherapy as a crucial part of their professional identity.[13] In the era of health care reform and the dominance of managed care, evidence-based medicine, and reimbursement systems based on brief Med Checks, psychiatric residency training has changed to embrace both long-term psychodynamic therapies and short-term, evidence-based psychotherapies.[14] Although training on dynamic psychotherapy remains a key component of psychiatry training, acquiring competency in other approaches is also required. Therefore, accreditation authorities and organizations generally oblige psychiatry residency programs to provide their residents the opportunity for the development of competency in various psychotherapy approaches.[14]

The *Accreditation Council for Graduate Medical Education* (ACGME) program requirements for graduate medical education in psychiatry (Effective July 1, 2014) imply that psychiatry residents should be trained to acquire competence in "applying supportive, psychodynamic, and cognitive-behavioral psychotherapies to both brief and long-term patient encounters, as well as to ensuring exposure to family, couples, group, and other individual evidence-based psychotherapies."[15] Likewise, the Royal College of Psychiatrists in the UK considers learning different types of psychotherapy including "brief therapy, cognitive behavioral therapy, psychodynamic therapy, psychotherapy combined with psychopharmacology, supportive therapy and all delivery systems of psychotherapy (that is individual, group, and family)" to be essential for psychiatric trainees,[16] Moreover, individuals who have completed their psychiatry core training can attend different fields of advanced training, including psychotherapy. After acquiring the necessary competencies, the participants of advanced training in psychotherapy are identified as 'specialists in psychotherapy.'[17]

Similar models of psychiatric training also exist in other countries. Based on residency curricula and programs in various countries, actual psychiatric practice, and the competencies required for psychiatrists, psychotherapy training can be considered as an indispensable part of psychiatric residency training. In fact, from the beginning of their training, psychiatry residents learn to obtain a psychotherapeutic understanding of their

patients, in the inpatient and outpatient settings, and have opportunities to use integrated treatments, combining pharmacological treatments and psychotherapy, to help the patients. In addition, during their psychotherapy training, the residents are compelled to attend particular theoretical courses and have direct clinical experience under close supervision of experienced faculty members. Such training provides the residents with clinical experience and helps them acquire the competencies necessary for different approaches of psychotherapy, including cognitive-behavioral, psychodynamic, and supportive psychotherapy. These approaches are practiced in different treatment settings such as individual, group, family, and couple therapies. However, different levels of expected competency are specified for the residents; while they are obligated to become competent in some cases, e.g. individual therapy of non-complicated patients through different approaches, they may only observe group and family therapies, based on the available resources of residency programs. Residents who are more interested in psychotherapy will find ways to gain maximum experience from the available facilities.

Conclusion

Psychotherapy is an essential part of the professional identity of psychiatrists. Many young physicians prefer to enroll in graduate medical education in psychiatry in order to learn and practice psychotherapy in their future career. Despite advances in biological psychiatry, neuroscience, and pharmacotherapy, psychotherapy is still recommended in clinical practice guidelines for different psychiatric disorders. Moreover, despite the fluctuations in the relation between psychiatry and psychotherapy, a great proportion of psychiatrists' time is devoted to provision of psychotherapy. Considering the dominance of biological psychiatry and neuroscience, development of various psychiatric medications, debates over the cost-effectiveness of different methods, and emphasis on evidence-based treatments in managed care-based health systems, contemporary psychotherapy is compelled to bridge its own concepts and methods with new findings, especially in the field of neuroscience. More studies with rigorous methodologies are also warranted to show the efficacy of various psychotherapeutic approaches in the treatment of different psychiatric disorders.

In the absence of adequate systematic information on the pattern of psychiatric training and practice in Iran, numerous surveys are needed to determine the level and pattern of psychotherapy practices by psychiatrists both in their offices and in hospitals. According to the latest approved national psychiatry curriculum,[18,19] a substantial part of psychiatry residency training is dedicated to psychotherapy training, and it is expected that residents become competent in applying different psychotherapy approaches. Nevertheless, further studies are required to provide systematic information about the domains, methods, and depth of psychotherapy training, and the expected level of competency at the end of the residency training in different programs. Such data on involvement of psychiatrists and other mental healthcare providers in providing psychotherapy in their clinical practice along with information on the current situation of psychotherapy training in these groups would undoubtedly be beneficial and necessary for future planning.

About the Faculty

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

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L903344

Multiple-Choice Questions

5. According to the lesson, the author postulates that:

A. randomized controlled trials can be used easily to evaluate psychotherapies, particularly long-term psychodynamic psychotherapy.

B. despite the advances in pharmacology, the role of psychotherapy in understanding the etiology and treatment of psychiatric disorders should not be neglected.

C. psychotherapy is not a crucial part of clinical psychiatry.

D. psychotherapy is outside the scope of biological treatment that is applicable to all fields of psychology.

6. According to the lesson, what is used as the 'gold standard' of evidence used to evaluate the effectiveness of psychotherapy?

A. Case report

B. Cohort study

C. Randomized controlled trials

D. None of the above

7. The decline in psychotherapy practice by psychiatrists in recent years can be attributed to:

A. changes in reimbursement policies.

B. the availability of psychiatric medications with few side effects.

C. the insurance companies' inclination to cover brief Med Checks.

D. All of the above

8. The ACGME program requirements imply that psychiatry residents should be trained to acquire competence in:

A. applying cognitive-behavioral therapy.

B. applying supportive, psychodynamic psychotherapy to brief and long-term encounters.

C. providing individual evidence-based psychotherapy.

D. All of the above

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Best Practices in CME

The Place of Psychotherapy in Contemporary Psychiatry

By Saman Tavakoli, MD

ID#: L903344

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

CME Lesson Overview

Recent advances in psychopharmacology and neuroscience, and growing dominance of managed care and evidence-based medicine have had dramatic impacts on health care delivery systems and clinical psychiatry practice. Despite these changes in the field of mental health, psychotherapy still remains a crucial part of clinical psychiatry and comprises a great proportion of psychiatrists' clinical practice.

Key Point 1: Overview

Psychotherapy remains a crucial part of clinical psychiatry and comprises a great proportion of clinical practice. Despite psychopharmacological advances, the role of psychotherapy in understanding the etiology of psychiatric disorders cannot be neglected.

Key Point 2: Efficacy of Psychotherapy

Common research methods and *randomized controlled trials* (RCTs) cannot easily be used to evaluate psychotherapies.

Key Point 3: Psychotherapy in Psychiatric Practice

Psychiatrists have the unique advantage of providing combination therapy by administering psychotherapy and prescribing medications which is a trend in current psychiatric practice.

Key Point 4: Contributors to the Decline in Psychotherapy in Psychiatric Practice

Changes in managed care reimbursement policies, the availability of psychiatric medications with few side effects, and the insurance companies' inclination to cover brief Med Checks all contribute to the reduction in psychotherapy provision by psychiatrists.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Exploring Psychosis and Bipolar Disorder in Women: A Critical Review of the Qualitative Literature

Anja Wittkowski, Laura K. McGrath, and Sarah Peters

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

KEY WORDS: Metasynthesis • Psychosis • Women • Mental health • Illness

LEARNING OBJECTIVES: This lesson presents a review of the literature concerning women's experiences with psychosis and bipolar disorder. As a result of reviewing women's feedback, clinicians will be more sensitive as they encounter such patients in their daily work and treatment planning.

LESSON ABSTRACT: Background: The experiences of women with severe mental illness warrant particular consideration to identify the strategies they use to facilitate recovery. This review systematically examined women's experiences of psychosis and bipolar disorder. Methods: Following an extensive database search, 13 studies met inclusion criteria. Noblit and Hare's metasynthesis approach was used to synthesize these qualitative studies exploring the experiences of 250 women, of which 78 (31.2%) were also mothers. Results: Twelve subordinate themes were identified and categorized into three overarching themes: (1) women's beliefs about illness, (2) perceived consequences of illness, and (3) strategies used to cope with illness. Contextual factors and spiritual beliefs were found to be important in these women's illness appraisals. Women incorporated diagnosis-related information into illness models if it was concordant with their existing beliefs. Conclusions: Women reported negative illness consequences relating to stigma, loss of self-determination and changes to relationships. They employed various strategies in order to cope with illness. Barriers to strategy use and clinical recommendations are presented.

COMPETENCY AREAS: This lesson presents a review of the literature concerning the beliefs of female patients suffering with bipolar disorder and psychosis. The literature reviews several themes such as (1) women's beliefs about illness, (2) perceived consequences of illness, and (3) strategies used to cope with illness. Upon the conclusion of the lesson, readers will appreciate the clinical recommendations of this study as they manage patients presenting with psychiatric disorders in the future.

Background

Extensive research has been undertaken exploring the experiences of people with mental illness.[1] Psychosis and bipolar disorder have been assigned to the general category of '*serious mental illness*' (SMI). Bipolar disorder is characterized by a primary disruption in mood. It is one of the leading causes of disability worldwide, affecting 1–1.5% of the population in the *United States* (US) and the *United Kingdom* (UK).[2] With alternating phases of mania and depression, bipolar disorder can have a serious impact on functioning.[3]

The most common diagnosis associated with psychosis is schizophrenia, which affects 1% of the population in all cultures. Symptoms include hallucinations and/or delusions, social withdrawal, flat affect and a loss of sense of pleasure and motivation.[4] Almost equal numbers of men and women are affected by psychosis, but onset is later for women.[5-7]

Initially, psychosis and bipolar disorder were assumed to be distinct clinical entities[8] but in recent guidelines[9] bipolar disorder is referred to as a psychotic disorder. Note: the term psychosis will be used throughout.

Evidence suggests that gender differences exist in the experience of mental illness. For example, women use mental health services more frequently than men and they desire a wider range of treatment options.[10] However, the diversity within women with mental illness has been overlooked.[11] Women's disadvantage within the mental health system interacts with other positions of disadvantage.[12] For example, exposure to risk factors for psychosis, such as abuse, is more likely to be found in women who are socially marginalized, such as those from lower economic status (SES) or *black and minority ethnic groups* (BME).[13]

While the impact of marginalization on risk factors has been well documented, there is evidence that mental health services respond to different groups of women in different ways, both in terms of accessibility of services and treatments received.[14] Societal attitudes towards women with mental illness compound this disadvantage. Stigma against people with mental illness has been named as one of the most important challenges for those experiencing such difficulties.[15] Goffman[16] identified two levels of stigma: the discredited and the discreditable. An individual with a mental illness would be viewed as discreditable because their undesirable attribute is not apparent to others initially and they can engage in behaviors designed to manage identity. In discredited individuals, stigma is apparent to others and cannot be concealed.

Finally, women's roles as wife, mother and carer of elderly relatives, as well as paid employee, need to be taken into account to understand the risk factors for mental illness and the consequences for women and their families.[17] Given the impact that psychosis can have on functioning, there is concern for women with a parenting role. It is estimated that internationally around 60% of women with SMI have dependent children and that the majority parent their children adequately.[18] However, some described significant difficulties,[19] without adequate support from health providers.[20,21]

When parenting is compromised, children's development might be affected. Although some children might not experience any difficulties,[22] children with a parent with SMI are at greater risk for developing a range of problems including relationship difficulties, mental illness, developmental delay and lower academic attainment.[23] Some women with SMI might be unable to maintain custody.[24]

Aims of the Study:

As it is important to consider the views of service users in developing policy and services,[25,26] the aim of this metasynthesis was to review qualitative research exploring women's experiences of psychosis and to extend the interpretative possibilities offered by the current literature, enabling a deeper understanding of their experiences and possible implications for recovery.

Method

Systematic Search:

The current metasynthesis included three stages: (1) A systematic literature search of qualitative studies reporting women's experiences of psychosis, (2) a critical appraisal of studies identified, and (3) the metasynthesis of these studies.

Published articles were identified through searches of the following databases: EMBASE (1980 to 2012), MEDLINE (1946 to 2012) and PsycINFO (1806 to

2012). The search terms in Table 1 were combined. The reference lists of all relevant articles were examined for additional studies that met the inclusion/exclusion criteria.

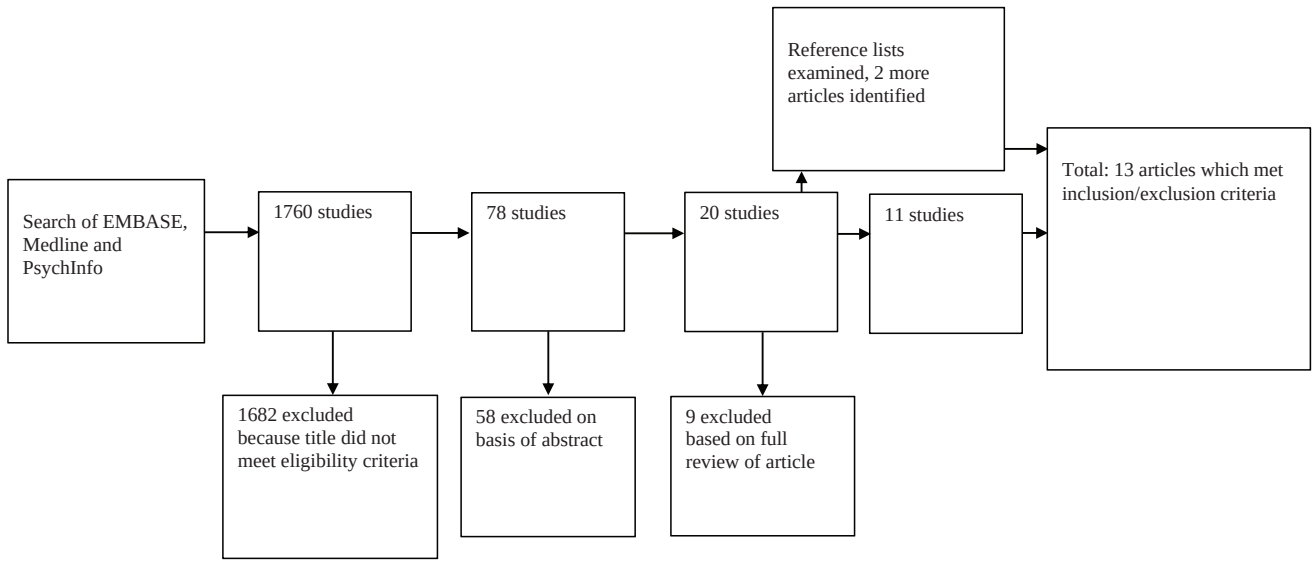
Table 1:
Final Search Criteria and Terms

Women	Psychosis or bipolar disorder	Qualitative research
Women	Serious mental illness	Qualitative research Grounded theory
Mother	Severe mental illness	Phenomenology Narrative
Mothers	Psychosis	Discourse Ethnography
Mothering	Schizophrenia	Thematic Interpretative phenomenology interview
Women Qualitative	Bipolar disorder Bipolar affective disorder	Focus group Explorative Observational Constant comparative

Inclusion and Exclusion Criteria:

The combined search strategy yielded 1760 studies. All titles were screened and studies were included them if they were written in English and used qualitative methods and data analysis to explore the experiences of women with psychosis. During screening, diagnostic categories that were considered to be indicative of psychosis included the following: psychosis, psychotic experience/symptoms, depressive psychosis, puerperal psychosis, schizophrenia, schizophrenic disorder, schizoaffective disorder, bipolar disorder and bipolar affective disorder. Articles which studied women with various diagnoses were included if at least 50% of the sample comprised women with experience of psychosis. Studies were excluded if structured questionnaires were used as the only method of data collection or if only quantitative data were reported. Mixed method studies were included if the results from the qualitative methods were reported separately. Studies that did not report data from women themselves were excluded. The majority of studies were excluded after an initial screen of the title indicated that they were not relevant. If relevance remained ambiguous, the abstract was reviewed. All potentially relevant studies were reviewed in full to determine eligibility (see Figure 1).

Figure 1:
Flow Chart to Illustrate Results of Search Strategy



Critical Appraisal:

We used the *Critical Appraisal Skills Programme* (CASP) criteria,[27] augmented by guidelines constructed by Walsh and Downe,[28] to assess the quality of the identified studies. Each study was allocated a total score out of 10 and a corresponding classification. Studies in Category A received a score of at least 9 and were deemed to have a low risk of bias. Studies in Category B (scores between 6 and 8) were deemed to have a moderate risk. Studies (<6) were assigned to Category C and were deemed to have a high risk of bias.

An independent rater checked the studies using these criteria. The raters were in 89% agreement. When disagreement occurred, scores were reassigned following discussion. Scores for two of the 13 articles were adjusted, which did not affect the categories to which they were assigned.

All identified studies were included because even studies with less rigorous methodologies can be valuable in the synthesis process.[29]

Metasynthesis Analysis:

Noblit and Hare's[29] method was used because it is one of the most developed and frequently used.[30,31] It allows for the preservation of the interpretative properties of primary data. Themes (i.e., third order constructs) are built from second order constructs, which are the views and interpretations of the authors expressed in terms of themes and concepts.[31] Tables, in which second order constructs from each article were illustrated by raw data in two columns, were explored for similarities, differences and relationships between the data. The following techniques were employed: (1) Reciprocal translation where concepts were translated into one another, (2) refutational translation, where contradictions between concepts were explored and finally, (3) synthesis of the translations to create overarching themes to explain the phenomena in the studies. In this iterative process, the phases described are not distinct but overlap and are repeated with progression of analysis.[29-31]

Results

Quality Assessment:

Thirteen articles met the inclusion criteria (see Table 2). Five[32-36] of the 13 studies were based in the US, four[37-40] in Canada, three[41-43] in the UK, and one[44] in Japan. All of the studies used interviews to generate data, including semi-structured (n = 5),[33,34,36,38,39] in depth (n = 2)[35,40] and narrative (n = 2).[37,43] In the remaining four studies,[32,41-43] the type of interview was not specified. Two studies used observational methods to collect additional data.[34, 36] Across the 13 studies, the experiences of 250 women were reported. Only nine studies reported the ages of participants (range: 21–73 years). Seven studies focused on women regardless of parental status, whereas six focused exclusively on mothers (n = 78, 31.2%). However, of the seven studies that focused on women, only two of them specified parental status.

Table 2:
Study Characteristics of 13 Studies

	Authors	Year	Country	Description of sample	N	Women/ mothers	Ethnicity	Recruited from	Data collection	Analysis	Score & quality rating
1	Hagen & Nixon [37]	2011	Canada	Women recovered from some form of psychotic experience. Diagnoses not stated. Age range: 27–57 years (mean: 38). No information about parental status. No information about level of education, religion, relationship status or SES.	18	Women	Not stated	Word of mouth/ advertise-ment in alternative health magazine	Narrative interviews	Phenome-nological data analysis	7 B
2	Borba et al. [32]	2011	USA	Women with diagnosis of SMI (10 schizophrenia, 6 BD, 13 major depression and 1 other). Sample described as low income, urban women. Age range: 28–62 years (mean = 45.8). No information about parental status. Highest level of education: Less than a high school diploma (10), high school diploma (16), some college credits (4). Religion not stated. Marital status: Married or living as married (2), widowed (4), separated (3), divorced (7), single, never married (14). No information about religion.	30	Women	28 African American 1 White, 1 other.	Community settings	Interviews	Modified constant comparative method	8 A
3	Venkataraman & Ackerson [33]	2008	USA	Mothers with BD. Age range: 21–49 years (mean not stated). Education: High school (5), college (5). Relationship status: Single (6), married (1), cohabiting (3). SES: Low (7), middle (3). No information about religion.	10	Mothers	White American	Community settings	Semi-structured interviews	Constant comparative analysis	6.5 B

Table 2 Study characteristics of 13 studies *(Continued)*

4	Luhrmann [34]	2008	USA	Homeless women with psychotic symptoms. No formal diagnostic interview. Ages not stated. No information about parental status. No information about education, religion, or relationship status.	61	Women	Not stated	Community settings	Semi-structured interviews/ observation	Not stated	5.5 C
5	Ueno & Kamibeppu [44]	2008	Japan	Mothers with chronic mental illness (13 schizophrenia, 7 mood disorders). Age range not stated. (mean: 43). Relationship status: Married (14), separated or divorced (4), widow (1), never married (1). No information about education, religion or SES.	20	Mothers	Japanese	Discharged inpatient/ community settings	Narrative interviews	Modified grounded theory	7.5 B
6	Chermonas, Clarke & Marchinko [38]	2008	Canada	Women with schizophrenia (9 schizophrenia, 3 schizoaffective disorder & 2 paranoid schizophrenia). Age range: 40–73 years (median: 45). No information about parental status. Education: Less than high school (4), completed high school (2), completed or some post-secondary education (8). Marital status: Married or living common law (3), single or divorced (9), have boyfriends (3). SES: Low (8), middle (4), high (2). No information about religion.	14	Women	Most White/White with European Ancestry, 1 part Aboriginal, 1 Asian.	Community settings	Semi-structured interviews	Not stated	6.5 B
7	Padgett et al. [35]	2006	USA	Formerly homeless women with SMI (5 schizophrenia, 2 schizoaffective disorder, 3 major depression, 3 BD). Age range: 31 – 62 years (mean: 50 years). 7 mothers. SES: Poor/working class (8), middle class (5). No information about education, religion or relationship status.	13	Women	6 African American 5 White, 2 Latina	Community settings	In depth life history interviews	Cross case/ collective case study	9.5 A
8	Chiu et al. [39]	2005	Canada	Women with SMI (18 schizophrenia or schizophreniform disorder, 6 major depression, 4 BD, 2 major depression with psychosis/delusions). Age range: 26–67 years (mean: 46). No information about parental status. East Asian women: Education: Elementary school (1), high school (6), post-secondary education (7), no formal education (1). Religion: Christianity (7), Buddhism (2), Catholicism (1). Relationship status: Single (6), married (3), widowed (2), divorced (2). SES: Self-employed (2), on pension (2), welfare or disability (9), supported by families (2). South Asian women: Education: Elementary school (2), high school (5), post-secondary education (4), no formal education (4). Religion: Sikhism: 15. Sikhism with Hinduism: 2. Relationship status: Married (7), widowed (3), separated (2), divorced (3). SES: Employed (1), welfare or disability (5), supported by families (9).	30	Women	15 East Asian 15 South Asian	Community settings	Semi structured interviews	Constant comparative analysis	9.5 A
9	Edwards & Timmons [41]	2005	UK	Mothers with postnatal illness (3 puerperal psychosis, 2 severe postnatal depression, 1 depressive psychosis). Ages not stated. No information about education, religion, relationship or SES.	6	Mothers	Not stated	Discharged inpatient	Interviews	Not stated	7.5 B
10	Diaz-Caneja & Johnson [42]	2004	UK	Mothers with SMI (8 schizophrenia, 10 BD, 4 severe depression with psychotic symptoms). 2 mothers 20–29 years, 9 mothers 30–39, 11 mothers 40+. Marital status: Currently married/living with partner (3), previously married, now not living with partner (11), widow (1), never married (7). No information about education, religion or SES.	22	Mothers	13 White UK, 3 White other, 1 Black UK, 1 Black Caribbean, 1 Black African, 2 Asian, 1 Mixed	Community settings	Interviews	Thematic analysis	8.5 B
11	Robertson & Lyons [43]	2003	UK	Mothers with experience of puerperal psychosis. Age range 28–44 years (mean = 34). No information about education, religion, relationship status or SES.	10	Mothers	Not stated	Community settings	Interviews	Grounded theory	6 B
12	Pentland et al. [40]	2003	Canada	Aging women with schizophrenia (45+ years, diagnosis of schizophrenia in early adulthood). Age range: 47–65 years. 3 mothers. Marital status: Married (1), divorced (1), single (4). No information about education, religion or SES.	6	Women	Not stated	Community settings	In depth interviews.	Thematic analysis	6.5 B
13	Sands [36]	1995	USA	Mothers with SMI – single, low income mothers with chronic mental illness living in a supportive residential programme. (6 schizophrenia, 1 schizotypal personality disorder, 1 major depression, 1 BD, 1 unknown.) Age range: 22–40 years (mean = 27). Education: At least high school education (6), less than high school education (3), unknown (1). No information about religion.	10	Mothers	7 African American, 3 White	Community settings	Semi-structured interviews/ observation	Not stated	5.5 C

Of the 250 women, 80 experienced psychosis, 77 schizophrenia and 34 bipolar disorder. Their diagnoses included the following: Psychosis (32%), puerperal psychosis (5.2%), schizophrenia (30.8%), bipolar disorder (13.6%), schizoaffective disorder (2%), major depression (10%) of which two women had severe postnatal depression, depression with psychotic symptoms (2.4%), schizotypal personality disorder (0.4%), and mood disorders (2.8%). In two cases (0.8%) diagnosis was not specified.

Three studies were assigned to Category A, eight to Category B, and two studies to Category C. Although all studies were included in the metasynthesis, the findings reported in articles assigned to Categories B and C were considered with more caution than those assigned to Category A. During the critical appraisal process, several weaknesses were commonly found. A detailed description of the sample and consideration of reflexivity were often lacking. Only eight of the 13 articles provided information about ethnicity and marital status of participants, seven included information about SES, five presented information about level of education and only one article provided information about religion.

Synthesis:

Three overarching themes were identified (see Figure 2): (1) women's beliefs about their illness, (2) perceived consequences of illness, and (3) strategies used to cope with illness. Contextual factors and spiritual beliefs were found to be important themes in how women understood their experiences. Information related to diagnosis was incorporated into women's models of illness only if it was concordant with their existing models. Women varied in the extent to which they accepted this information and found it useful. Women noted the negative consequences of their illness in relation to stigma, loss of self-determination and changes to relationships. These consequences interacted with one another and became ongoing contextual factors for women. They employed various strategies to cope with their illnesses. While the use of particular strategies augmented the use of others, in some cases strategies conflicted with one another. Strategy selection was driven by women's beliefs about their illness and fear of consequences. Women discussed further changes in their relationships, which they attributed to their use of strategies (see Figure 2). Table 3 illustrates the third order categories noted in the identified 13 studies.

Figure 2:
A Diagrammatic Representation of the Synthesis of Articles

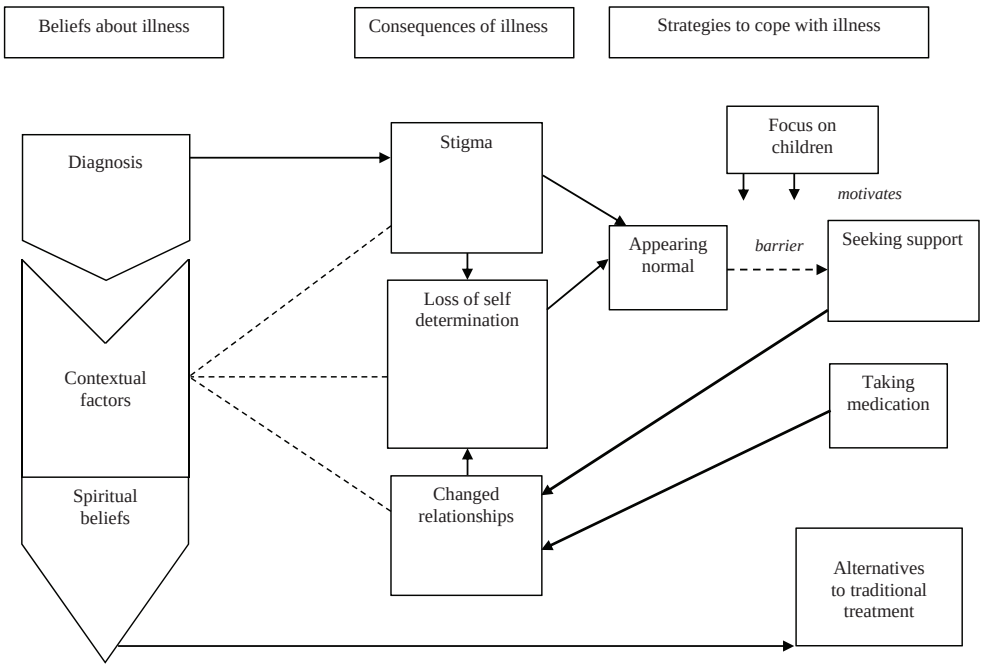


Table 3:
Studies Illustrating Third Order Constructs

	1 Hagen & Nixon	2 Borba et al.	3 Venkataraman & Ackerson	4 Luhrmann	5 Ueno & Kampibeppu	6 Chermonas et al.	7 Padgett et al.	8 Chiu et al.	9 Edwards & Timmons	10 Diaz-Caneja & Johnson	11 Robertson & Lyons	12 Pentland et al.	13 Sands
Beliefs about illness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Contextual factors	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Spiritual beliefs	Yes	No	No	No	No	No	No	Yes	No	No	No	Yes	No
The role of diagnosis	Yes	No	No	Yes	No	No	No	No	Yes	No	No	No	No
Consequences of illness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stigma: Feeling misunderstood/ judged	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Loss of self-determination	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Changes to roles/relationships	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Strategies to cope with illness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Focus on children	No	No	Yes	No	Yes	No	No	No	No	Yes	No	No	Yes
Seeking social support	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Seeking support from professionals	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Appearing "normal"	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	Yes	No	No
Taking medication	No	No	No	No	No	No	No	Yes	No	Yes	No	No	Yes
Alternatives to conventional treatment	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Yes	No

Theme 1: Beliefs about Illness:

Contextual Factors

Women believed that it was not possible to understand their experience of mental illness without reference to contextual factors.[37] The opportunities and difficulties, which women experienced, were strongly related to the social context in which they found themselves. Women's social contexts included culture, religion and *socioeconomic status* (SES). A complex interaction between these factors and experiences including abuse and substance use, disruptive life events including loss of residence, and the need to fulfill role expectations, were noted.[35] For example, white and middle class women were more likely to have substance abuse problems than their African American and working class counterparts.[35] In addition, women who had somewhere to live that they perceived to be safe, had a stronger sense of personal agency.[35]

Our synthesis also highlighted that the experience of immigration was important. Striving to fulfill role expectations was particularly pertinent for immigrant women who were required to adjust to new countries with different values and role expectations: "*I got mentally sick because I was made to do a lot of household chores here. I have to look after four children plus do household chores. There was nobody to help me….*"(p. 638) 39

Women came to understand that they had a responsibility to care for themselves[42] to remain able to care for their families.[44] Indeed women who were in a position to relinquish responsibilities associated with raising a family and engaging in paid employment discussed feelings of liberation.[37] Greater choice in relation to these responsibilities was mediated by factors, such as SES, culture and level of social support. For example, cultural differences existed in the nature of expectations for women to take up paid employment and share responsibility for raising children.[39] Further, the financial implications of loss of income were larger for women from lower SES groups, with lower levels of social support.[32] In addition to the role of contextual factors, some women held a stress-vulnerability model[45] of mental illness in which contextual factors caused illness in those with personal characteristics that rendered them vulnerable: "Some people cannot handle the pressure… They break and become mentally ill."(p. 16) 34

Women spoke of social isolation as an important factor contributing to and exacerbating their difficulties. Women discussed that professionals often ignored the impact of contextual factors in understanding their

illness and their lives,[37] which created a barrier to women seeking support from them: "If you don't say, they don't ask."(p. 477) [42]

In contrast to women in other studies, the participants in one study[43] saw "the cause of their illness as biological."(p. 418) This finding might be explained by the fact that women were experiencing psychosis in the context of childbirth for which there is more evidence of a biological aetiology. However, because of methodological concerns associated with this study, this finding was given less weight.

Spiritual Beliefs

Spiritual beliefs played a role in women's models of mental illness,[37] particularly the case for immigrant women. Ideas about the meaning of mental illness "varied with each person and from one culture to another."(p. 645) [39] Women expressed representations of their experiences, which were directly related to their religious convictions, such as "a bad spirit resided in me."(p. 648) [39] or "a moving of energy."(p. 58) [37] This impacted on women's interpretations of their symptoms mediating the distress caused. For these women, it was not possible to recover until they had given due consideration to these factors,[37] and often coping strategies were borne out of this understanding. Women found that a lack of interest and understanding from professionals regarding their spiritual beliefs was a barrier to seeking support.[37]

The Role of Diagnosis

Women varied in their willingness to accept a diagnosis as part of their understanding of mental illness, which appeared to depend on whether or not a diagnosis was concordant with their existing model of mental illness. Women felt reassured and relieved that their symptoms were recognized as an illness, which could be treated:[41] a diagnosis could facilitate access to appropriate support and useful medication. However, some women actively avoided assessment and diagnosis despite potential benefits. For some, a lack of consideration of contextual factors or spiritual beliefs by health professionals rendered labels "meaningless."(p. 52) [37] Luhrmann[34] discussed the importance of attempting to understand the meaning of a diagnosis within the context of the woman's particular social world. Even for women who assimilated a diagnosis into their understanding of mental illness, they acknowledged stigma associated with this label.[41]

Theme 2: Consequences of Illness:

Stigma: Feeling Misunderstood/Judged

In relation to stigma associated with mental illness, women discussed the experience of perceived stigma from others[41, 42] and self-stigma,[39] including the restrictions of roles available to them resulting from stereotyping. This restriction contributed to their experience of social isolation.[38] However, women acknowledged that stigma associated with mental illness varied with culture: "*The biggest comfort is that I am in Canada. It's much better than in China. People like us in China would be stoned and stepped upon*"(p. 641) [39]

Fear of stigma and the associated negative reactions of others motivated women to appear "normal", which posed a barrier to seeking support both from informal support networks and professionals. Women's fear of stigma was attenuated in relating to others who had experienced mental illness themselves.[43]

Loss of Self-determination

Women discussed a loss of self-determination during periods of illness, particularly in relation to hospitalization, when they perceived "having one's freedom stripped away,"(p. 55) [37] treatment[43] and threat of custody loss.[41] Loss of self-determination was associated with feeling "overwhelmed and powerless."(p. 56) [37] Fear of loss of self-determination motivated women to appear "normal"[32] and prevented them seeking professional support.

Women also discussed a "lack of control" (p.289) over the contextual aspects of their life experience, such as abuse, financial disadvantage and drug use.[32] They spoke of the loss of being able to live independently[40] and dissatisfaction with the requirement to submit to restrictions imposed by providers of accommodation.[34-36] However, women expressed ambivalence as they also spoke about the benefits of "having their daily needs met without having to worry."[40]

Changes to Roles/Relationships

Women discussed changes to their relationships, which occurred as a result of their illness. Feelings of isolation led to power imbalances in relationships and associated

vulnerability to "emotional and physical victimization."(p. 288) [32] Women often felt that they had no choice but to remain in such relationships: "Sometimes we fight and he'll get my schizophrenia involved…It makes me feel like I don't know how to do anything…I feel defensive…I always say, '*I'm not staying here anymore. I'm going to leave', but I never do.*"(p. 445) [38]

After illness onset, women felt unable to fulfill certain role expectations;[40] trying to maintain certain roles contributed to stress and illness exacerbation.[39] Women described that relationships which had been happy previously, became strained[43] and sometimes broke down completely.[32, 40]

Mothers worried about the impact of their illness on their children.[44] Some acknowledged an "unhealthy dependency"(p. 394) [33] on their children during periods of illness and that children had taken on age-inappropriate responsibilities.[42] Mothers also recognized that symptoms[33,40,44] and medication,[39, 42] had an impact on their ability to parent effectively. These factors led to feelings of guilt, which motivated compensatory styles of parenting. Outcomes included inconsistent parenting practices, resulting in behavioral problems in children,[33] which contributed to stress levels in mothers. Women who had lost custody of their children discussed the "emotional trauma"(p. 90) [36] associated with this loss.[32, 40]

Theme 3: Strategies to Cope with Illness:

Focus on Children

Women who were mothers described this role as rewarding and central to their lives.[36] They discussed that their children were a powerful incentive to recover and remain well.[44] This included motivating women to continue using other strategies that they perceived to facilitate this process; for example, continued engagement with professionals.[42]

Seeking Social Support

Seeking social support was cited as an important factor in women's ability to cope with mental illness.[38, 40] Women valued having someone trustworthy to confide in who could provide practical and emotional support: "*He's a very supportive person; he loves me; and things that I feel I have to keep secret, I can talk to him about.*"(p. 445) [38] Beliefs that their problems were exacerbated by social isolation motivated them to seek social support. However, barriers to accessing social support included an inability to be open about their experiences. Some were unable to work because of their illness so did not have this forum to meet people.[38, 40] Women expressed the view that resources were inadequate to support them to continue with family and social life,[39] leading to further family breakdown and social isolation. Women whose experiences had led them to believe they were "able to rely on few others for protection" were less likely to seek support.(p. 17) [34] Cultural differences affected the ways in which women used social support. For example, self-reliance in making treatment choices and the acceptability of separation or divorce from their spouse were factors that varied between cultures.[39]

Women discussed the benefits of seeking support from others with similar experiences,[30, 43] believing that they would have more understanding of mental illness, be less likely to react negatively and able to offer normalizing explanations. For some women this was the "most helpful part of their encounter with the mental health system."(p. 57)[37] However, women also discussed difficulties in depending on others with mental illness, including the inconsistency of this support. Women recognized that "the support they wanted was not available when their friends were ill"(p. 445)[38] or frequently changing their place of residence.[32]

Seeking Support from Professionals

Women discussed seeking support from professionals as an important aspect of coping with their mental illness.[40] This was particularly noted for women with impoverished social support networks: "*He's [psychiatrist] my biggest support…I can tell him my problems because he always listens.*"(p. 443) [38]

Barriers to seeking support from professionals included a fear of loss of determination, stigma[39] and feeling "invalidated and unheard" by professionals.(p. 53) [37] Women discussed that a lack of continuity of care discouraged the formation of trusting relationships with professionals.[38, 42] For women who had adapted to particularly hostile environments (i.e., homelessness), coping strategies were often in direct conflict with expectations of services.[34] Women who were parents discussed that this aspect of their lives was often ignored by professionals and that they needed more support in their parenting role.[33] An exception to this was in the study by Sands[36]

who reported that although observations revealed that mothers "had difficulty attending to or disciplining" their children, they "did not acknowledge this need directly" and "acted as if they did not need help and had nothing to learn from the staff."(p. 93) [36] A possible explanation for this was fear of custody loss associated with greater openness about their difficulties. However, less weight should be given to this finding because of the study's low quality.

Appearing "Normal"

Appearing "normal" to others was driven by a fear of losing self-determination, particularly in relation to hospitalization and custody loss. Appearing "normal" allowed women to avoid hospitalization because "when you started saying the right things, you would be considered better." (p. 55) [37] This strategy was also driven by fear of stigma. For women who lived in more threatening environments (e.g., homelessness), appearing "normal" was a survival strategy because they believed that showing any sign of vulnerability would attract people who would take advantage of them:[34, 35] "You have to keep your guard up at all times."(p. 17) [34]

Women frequently moved house to hide their illness, contributing to social isolation.[32] Even women who viewed themselves as recovered from mental illness engaged in suppressing normal emotions driven by a fear that these would be viewed as pathological by others: "*I was really conscious that you're allowed…the blues…and I was thinking God even if I have that will they think I'm going downhill and put me on drugs.*"(p. 423) [43]

In addition to appearing "normal" to others, women also distanced themselves from others with mental illness:[43] "*I can remember being in hospital…and I used to look at the other patients and think "blooming heck" what is up with them…and I was just as bad [she laughs].*"(p. 476)[41] For women whose illness was of a less chronic nature, the need to appear "normal" and to separate themselves from others with mental illness declined as they recovered. This was replaced by a desire to be open about their experience with the aim of reducing stigma.[41] It is possible that talking about their experiences enabled women to develop a narrative which facilitated their understanding of the experience and hence their recovery.

Taking Medication

Women acknowledged the value of taking medication.[36] However, this was often an understanding that developed over time. Taking medication did not exclude the use of other strategies to cope. Women viewed strategies as serving different but complementary functions: "*When I do meditation, I feel relaxed and my stress goes away. That's the help I am getting from spirituality…medicine is also needed. Spirituality has its own values and medicine has got its own…both work hand in hand, not alone.*"(p. 648)[39]

Alternatives to Conventional Treatment

Women looked to sources other than the traditional mental health system to supplement their coping strategies.[37] Spirituality and belief systems were closely related to women's choice of strategy selection.[39] Alternatives to traditional treatment included but were not limited to spirituality, religious practices, Reiki and yoga. For example, immigrant women engaged in culture-specific practices that often existed alongside engagement with conventional treatments.[39] Women discussed many benefits of spirituality including empowerment,[35] acceptance, wisdom and strength: "*I don't think if I didn't have God, I don't think I could get through my life.*"(p. 296) [40]

Discussion

This is the first attempt to systematically explore the qualitative literature on the experiences of women with psychosis. Three overarching themes emerged and a model was developed to explain their experiences.

Women appear to construct idiosyncratic illness models of their experience, which did not necessarily incorporate information from dominant biomedical paradigms of mental illness. This is concordant with data suggesting that individuals' understanding of their problems, rather than labels/diagnoses, have a strong mediating influence on how they view themselves in relation to mental illness.[1, 46]

Women were critical of health care professionals ignoring contextual factors in their lives. This is reminiscent of the feminist critique: labeling women as mentally ill hides injustices including social inequalities.[12] Gender interacts with other relevant variables, such as race, ethnicity and socioeconomic status. Women from minority groups (e.g., immigrants)

are more likely than British born white women to experience mental ill health.[12] While racism, access to resources and social isolation might be important factors, there is evidence that their experience of the mental health system is different for these groups of women. For example, African-Caribbean women are more likely to be hospitalized on an involuntary basis and they are more likely to receive medication for mental distress.[47] The importance of the relationship between sociocultural factors with illness models has already been highlighted:[46] marginalized groups may be more likely to reject white, middle-class professionally conceived psychiatric explanations.

The way that mental health is conceptualized in western societies reflects underlying societal structures and relationships.[12] The mental health system reflects this bias and it has been argued that psychiatric care and treatment does not take account of spiritual belief systems and their role in coping with mental distress,[48] discussed by women in the current study. Religious beliefs might conflict with illness paradigms used by health professionals and could discourage engagement.[49] However, religion and spirituality might provide positive coping to people with bipolar disorder[49] and schizophrenia.[50]

The role of self-determination in influencing health and well being is well established. The failure to provide services, which preserve the self-determination of people with mental illness, has been reported elsewhere,[51] but this problem is particularly pertinent for women.[52] Although a focus on self-determination is an important component of recovery-oriented services, it has been argued that these concepts have not yet been established in the mental health system.[53] Reducing women's view that service involvement will inevitably lead to a loss of self-determination is likely to enhance engagement with services. Several recommendations have been made in the literature to help health professionals support the self-determination of people with mental illness, including a focus on individual preferences to inform decision-making[54] and paying attention to women's beliefs about their illness rather than dismissing them in favor of dominant biomedical models.[55]

Women reported that they believed an understanding of contextual factors to be imperative to understanding their mental illness and that professionals' minimizing of these factors discouraged engagement. The role of stress in precipitating psychosis has been established;[45] however, the link between contextual factors and psychosis might be particularly important for women because severe physical or sexual abuse was associated with psychosis in women but not men.[13]

Although stigma is common to all mental illnesses, it is greater for people with SMI.[56] Stigma is not unique to women, but there is some evidence that the effect of stigma might be greater for women, having a greater impact on their willingness to disclose problems[57] and seek support.[58] Goffman[16] realized that stigmatized people reveal or hide certain parts of themselves in order to influence the reactions of others, demonstrated by women in the current study using the strategy of appearing "normal." This strategy was driven by their beliefs about how others react to people with a mental illness in line with modified labeling theory.[59] Consistent with this approach, women who felt more threatened by the potential reactions of others were more motivated to hide their illness. Stigma and discrimination related to mental illness interact with additional inequalities related to gender and ethnicity to render some women doubly disadvantaged.[60]

Changes in relationships were related to the restrictions imposed on social support networks caused by illness. However, the strategies people use to manage the reactions of others, such as social withdrawal and non-disclosure, can have negative consequences for social support networks.[59] Furthermore, individuals with psychosis may have a poor understanding of the feelings and intentions of others.[61, 62] Thus, family members are not always equipped to provide the level of care needed by individuals with SMI.[63]

As the process of metasynthesis is inherently interpretative, introducing subjectivity and potential bias, transparency in the development of themes was emphasized.[64] In addition, the systematic identification of studies and critical appraisal by two independent raters enhanced the rigor of the metasynthesis. Finally, comprehensive details of the included studies were provided to enable the reader to consider the findings within the various contexts. However, information about ethnicity, class, level of education, religion, marital and parenting status and SES were often not provided, but future research should routinely provide comprehensive information about male and female participants, including their parenting

status. Notably, the majority of the participants in the 13 reviewed studies were described as poor.

As this metasynthesis focused solely on women's views, it would be important for future research to synthesize the views of men so that similarities and differences between experiences could be evaluated. Some of the themes identified in this review may apply to men.

The findings outlined here have several implications for ways in which services can optimize women's use of strategies for coping with mental illness. Given the importance of informal social support networks and the difficult changes in relationships that can occur as a result of illness, a family-centered approach should be taken to women's care, by educating and supporting family members and involving them in decision-making. Professionals should be provided with regular training around how to enhance women's engagement with services. Strategies might include ensuring continuity of care when possible, a more holisitic assessment of women's difficulties which encompasses contextual factors and spiritual beliefs and inclusion of women in decision-making. Reflection on the assumptions of healthcare professionals about male and female behaviors and how this influences practice should be encouraged in supervision. If women believe they are listened to by culturally sensitive services, women will be able to seek more support, optimizing their coping.

As some women are also mothers and parents, their well being, their child(ren)'s well being and that of the family should be inquired about, if possible assessed and, where necessary, appropriate and effective parenting interventions should be offered.[65, 66]

Conclusion

In summary, women with psychosis hold beliefs about their illness, which incorporate contextual factors and spiritual beliefs in addition to biomedical explanations. They developed adaptive strategies to cope with their illnesses, which can be understood in the context of their beliefs.

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

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AW came up with the literature search idea and provided supervision to LM who carried out the initial review. AW oversaw the overall metasynthesis and review process and the developing manuscript, particularly the final version. LG carried out the initial literature searches, the initial metasynthesis and provided the first draft of the manuscript. SP contributed to the supervision of the review process and provided input into the development of the manuscripts, including the final one. All authors contributed to and have approved the final draft.

BMC Psychiatry 2014, 14:281 doi:10.1186/s12888-014-0281-0

The electronic version of this article is the complete one and can be found online at: http://www.biomedcentral.com/1471-244X/14/281

Received: 21 November 2013

Accepted: 29 September 2014

Published: 18 November 2014

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Multiple-Choice Questions

9. According to the lesson, all of the following statements about women's mental health care are correct, *except*:

A. Women believed that it was not possible to understand their experience of mental illness without reference to contextual factors.

B. Women came to understand that they had a responsibility to care for themselves to remain able to care for their families.

C. Women who were able to relinquish familial and employment responsibilities reported greater feelings of liberation.

D. Women viewed other women seeking mental health care as selfish.

10. All of the following were found to be consequences of mental illness for many women, *except*:

A. fear of being stigmatized lead to a reluctance to seek professional or informal support regarding mental health issues.

B. feelings of losing one's autonomy or being judged as incapable prevented women from seeking support.

C. women found their relationships grew stronger in the face of adversity.

D. previously stable relationships became more strained.

11. According to the lesson, what are some factors that drive women's desire to appear "normal" when coping with a mental illness?

A. A fear of hospitalization

B. The possibility of losing custody of one's children

C. It is a survival strategy that keeps the individual from appearing vulnerable to danger.

D. All of the above

12. Why are women found to be critical of the ignorance of some mental health professionals regarding contextual factors that may influence mental illness?

A. Women believe that ignoring the context of their illness will prevent an accurate diagnosis of their illness.

B. By ignoring contextual factors, mental health professionals overlook the ways in which injustice can have an ill effect on an individual's mental well-being.

C. Women want sensitive practitioners who will protect them from life's difficulties.

D. The ignorance of contextual factors surrounding mental illness is correlated with increased long-term hospitalization.

Best Practices in CME

Exploring Psychosis and Bipolar Disorder in Women: A Critical Review of the Qualitative Literature

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ID#: L903345

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

CME Lesson Overview

The experiences of women with severe mental illness warrant particular consideration to identify the strategies they use to facilitate recovery. This review systematically examined women's experiences of psychosis and bipolar disorder. This lesson addresses several key points regarding the factors that may impede many women from seeking professional help, or even social support for their mental illnesses. This delay can contribute to worsening outcomes in treatment, not to mention additional distress and a lower quality of life for individuals. Outlined below are some of the key facts regarding the stigma surrounding seeking mental healthcare and the factors which contribute to it.

Key Point 1: Background

Mental health service providers respond to different groups of women in different ways, impacting not just a woman's ability to receive services, but the kind of services she receives.

Key Point 2: Contextual Factors

Contextual factors include culture, religion, and socioeconomic status affected the way women experience and understand mental illness.

Key Point 3: Management

Several randomized clinical trials of adjunctive pharmacological agents to antipsychotics have produced promising findings.

Key Point 4: Loss of Self-determination

Studies demonstrated that women have a fear of losing their freedom or losing custody of their children increased feelings of being power.

Key Point 5: Changes to Roles and Relationships

Following the onset of illness, women found that their roles in their relationships changed and that even previously happy partnerships became more tense.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Bipolar Disorder in Children, Part 1: An Overview

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

KEY WORDS: Bipolar Disorder • DSM-5 • Assessment • Mania • Pharmacotherapy • CBT

LEARNING OBJECTIVES: In this lesson, clinicians will (1) review the historical background of bipolar disorder in the literature, (2) compare and contrast the development of diagnostic criteria included in the *Diagnostic and Statistical Manual of Mental Disorder,* and (3) consider comorbid psychiatric disorders which may have overlapping symptoms in children with bipolar symptoms.

ABSTRACT: Although bipolar disorder historically was thought to only occur rarely in children and adolescents, there has been a significant increase in children and adolescents who are receiving this diagnosis more recently (Carlson, 2005). Nonetheless, the applicability of the current bipolar disorder diagnostic criteria for children, particularly preschool children, remains unclear, even though much work has been focused on this area. As a result, more work needs to be done to further the understanding of bipolar symptoms in children. It is hoped that this paper can assist psychologists and other health service providers in gleaning a snapshot of the literature in this area so that they can gain an understanding of the diagnostic criteria and other behaviors that may be relevant and be informed about potential approaches for assessment and treatment with children who meet bipolar disorder criteria. First, the history of bipolar symptoms and current diagnostic criteria will be discussed. Next, assessment strategies that may prove helpful for identifying bipolar disorder will be discussed. Then, treatments that may have relevance to children and their families will be discussed. Finally, conclusions regarding work with children who may have a bipolar disorder diagnosis will be offered.

COMPETENCY STATEMENT: This lesson will help clinicians gain an understanding of diagnostic criteria in the assessment of bipolar disorder in children. Children presenting with bipolar symptoms often present with overlapping symptoms of other comorbid childhood psychiatric disorders. Upon completion of this lesson, clinicians will be better equipped to consider the similarities in the assessment of these symptoms as well make treatment recommendations utilizing medication and psychotherapy.

Bipolar Disorder in Children

Although bipolar disorder historically was thought to only occur rarely in children and adolescents, there has been a significant increase in children and adolescents who are receiving this diagnosis currently.[1,2] **In fact, a recent meta-analysis suggested that the overall occurrence of bipolar disorder in children and adolescents was 1.8%.[3]** Nonetheless, the applicability of the current bipolar disorder diagnostic criteria for children, particularly preschool children, remains unclear, even though much work has been focused on this area. As a result, more work needs to be done to further the understanding of bipolar symptoms in children. It is hoped that this paper can assist psychologists and other health service providers in gleaning a snapshot of this diagnosis so that they can gain an understanding of the diagnostic criteria and other behaviors that may be relevant and be informed about potential approaches for assessment and treatment with these children. First, the history of bipolar symptoms and current diagnostic criteria will be discussed. Next, assessment strategies that may prove helpful for identifying bipolar disorder will be discussed. Then, treatments that may have relevance to children and their families will be discussed. Finally, conclusions regarding work with children who have a bipolar disorder diagnosis will be offered.

History of Bipolar Disorder

Although the identification of bipolar symptoms (i.e., depression and mania) may be relatively recent in children, the identification of these symptoms is certainly not new. In fact, depression and mania appear to be the world's first documented mental illnesses,[4] tracing back to ancient Greece.[5] For example, Hippocrates considered melancholia (i.e., depression) and mania to be among the earliest diagnosable disorders. In the first century A.D., the Greek physician Aretaeus of Cappadocia combined these two groups of symptoms into bipolar disorder by stating that mania was a worsened state of melancholia (rather than suggesting that mania and melancholia were distinct][4]). In Aretaeus' texts *On the Aetiology and Symptomatology of Chronic Diseases* and *The Treatment of Chronic Diseases*, sufferers of melancholia were depicted as quiet or dysphoric and sad or apathetic, and sufferers of mania were depicted as cheerful.[4] Other references did not draw a connection between melancholia and mania until the seventeenth century; however, for example, Théophile Bonet began using the term *melancholicus mania* in 1679[6] and Willis described melancholia and mania as *distempers of raving* in his writing.[7]

Following these initial references to bipolar symptoms, advancements in the classification of bipolar disorder generally did not occur until the 19th century. For example, in 1851, a new reference to bipolar disorder was made. At this time, French psychiatrist Jean-Pierre Falret conceptualized bipolar disorder as being cyclical in nature, referring to this phenomenon as the *folie circulaire* (i.e., circular madness). Falret described manic and melancholic episodes that were separated by symptom-free intervals.[4,5] In 1854, French psychiatrist Jules Baillarger also described the cycling of manic and melancholic symptoms (i.e., *folie à double forme*), but without the presence of symptom-free intervals.[4,5] Although Falret and Baillarger disagreed on the exact nature and cyclical process of bipolar disorder, they both agreed that the diagnosis and prognosis of this disorder was "desperate, terrible, and incurable."[8, p405] This early thinking allowed for bipolar disorder to be accepted throughout Europe.

During the end of the 19th century and the beginning of the 20th century, Emil Kraepelin employed a unifying approach to the classification of mood disorders, resulting in bipolar disorder being subsumed within the category of *manic-depressive insanity* (MDI). MDI included *circular insanity* and unipolar disorders (e.g., single-episode and recurring depression.)[9] Unlike previous descriptions of bipolar symptoms, the diagnosis of MDI had a good prognosis.[9] Although Kraepelin suggested that bipolar disorder was a severe mental illness, he also suggested that individuals with this diagnosis experienced mild residual states after recovery from individual episodes and mild fluctuations between episodes. It is also noteworthy that Kraepelin referred to the possibility of manic depression occurring in children, although rarely.[10]

Because Kraepelin's unification of mood disorders was so widespread, further research on the course of

these disorders failed to differentiate between depression, mania, and bipolar disorder.[11] Nonetheless, there were many psychiatrists who opposed Kraepelin's idea of merging mood disorders into one category. In particular, German psychiatrists Wernicke,[12] Kleist[13] and Leonhard[14] described subtle differences in various mood syndromes and described them as separate entities. Together, Kleist and Leonhard gathered data on family history and clinical course to support the distinction between *bipolar disorders* and *unipolar disorders.*[9] This information would not be taken seriously in psychiatry until 1966, the year referred to as the "rebirth" of bipolar disorders[15] due to the publication of two important works.

These works were Angst's[16] monograph and Perris and d'Elia's[17] article.[15] Both works suggested that genetics played a role in the etiology of endogenous depression, that bipolar disorder was represented equally in males and females, that manic-depressive illness was not homogenous (i.e., unipolar depression differed significantly from bipolar disorder), and that unipolar depression had a strong genetic relationship to bipolar disorder.[15] These works, along with research completed by Winokur and colleagues,[18] confirmed the findings postulated by Kleist and his colleagues. As a whole, these works contributed to the increased interest in and knowledge of bipolar disorder in the 20th century.

With regard to theorizing about bipolar symptoms in children, psychoanalytic theorists, such as Adolf Meyer, Karl Abraham, and Melanie Klein, were some of the first to make references to manic-depressive symptoms in children (see ref. 5, for a summary). In fact, child psychiatrists began to examine bipolar symptoms in their patients, looking for presentations that resembled those seen in adults. Case studies then began to suggest that bipolar symptoms in children were rare and that, if these symptoms did occur, they generally did not occur until late adolescence.[5] In contrast, some psychiatrists suggested that mania was being overlooked in children because of the overlap between manic symptoms and those of other disorders (e.g., *attention-deficit/hyperactivity disorder* [ADHD]) and because of the appearance of manic symptoms in children who were developing typically. Although group studies and other studies of bipolar symptoms in children were documented by a variety of researchers starting in the 1920s, Anthony and Scott[19] concluded in a systematic review of the literature that manic depression was rare in childhood.

Beginning in the 1970s, however, interest in understanding and identifying bipolar disorder in children experienced a resurgence (see ref. 5). For example, Weinberg and Brumback[20] created criteria to diagnose mania in children. These criteria, which included symptoms of euphoric or irritable mood, hyperactive behavior, and flight of ideas, served as the basis for the *DSM-III* bipolar disorder criteria. **Since 1980, *DSM* criteria have specified that adult criteria can be used to diagnose mania in children, with modifications based on differences in age and developmental stage.[21]** Consequently, by the early 1980s, there was an increasing acceptance that children could present with bipolar symptoms. For example, Carlson[22] suggested that children with mania were described as exhibiting hyperactivity, an absence of discrete episodes, more irritability and emotional lability (as opposed to euphoria), and a relative lack of paranoia or grandiosity. Additionally, children who were experiencing the depressive phase of the disorder were thought to not display specific depressive episodes. Instead, they were described as being agitated or irritable in the same way as children with unipolar depression. Further, children who were older than 9 years of age were described as presenting with a more classic pattern of symptoms that was marked by discrete episodes, euphoria and irritability, and grandiosity.[22]

Nonetheless, bipolar disorder still remains controversial for children. For example, the World Health Organization United States/United Kingdom study of manic depression and schizophrenia[23] showed that these two English-speaking countries made vastly different diagnoses for the same constellation of symptoms, prompting an increased interest in operationally defining criteria for these diagnoses. More recent research suggested that such findings still occur consistently, as research using case vignettes suggested that mental health professionals in the United States still are more likely to assign a bipolar disorder diagnosis than those in the United Kingdom.[24]

Consequently, structured and semistructured interviews were developed, and researchers began to depend

more on standardized criteria for diagnoses, using symptoms such as those in the *Research Diagnostic Criteria*[25] and the *Diagnostic and Statistical Manual of Mental Disorders.*[26-30] With the increased importance of defining criteria and the decreased specificity of the definition of *episode* in the *DSM-III-R*, the diagnosis of bipolar disorder became symptom driven in 1987. In contrast, the initial appearance of bipolar disorder in the *International Classification of Diseases (ICD)* defined the disorder in broader terms and focused on the whole picture of episodes or the course of the illness.[31] Thus, more clarity is needed.

Bipolar Disorder Symptoms in the *DSM-IV-TR*

Until recently, the criteria that were described in the *DSM-IV*[28] and *DSM-IV-TR*[29] were used to diagnose bipolar disorder in the United States, with bipolar disorder being listed as a mood disorder (similar to the rubric proposed by Kraepelin).[10] In fact, there were several different diagnoses in the *DSM-IV-TR* bipolar diagnostic grouping, each made in conjunction with the presence of manic, mixed, or hypomanic episodes. **A manic episode was identified when individuals experienced an episode of elevated, expansive, or irritable mood that lasted for at least one week (the duration could be less than one week if hospitalization was necessary.)[29] This episode was accompanied by three or more symptoms (from seven provided symptoms) when the individual's mood was elevated or expansive and by four or more symptoms when the individual's mood was irritable. These symptoms could include grandiosity, a decreased need for sleep, pressured speech, flight of ideas or racing thoughts, distractibility, increased goal directed activity or psychomotor agitation, and excessive participation in pleasurable but risky activities. These symptoms had to cause severe impairment in functioning and could not be due to a substance or a general medical condition.[29]**

In contrast, for a mixed episode, individuals had to experience symptoms consistent with both a manic episode (as described above) and a depressive episode (with either depressed or sad mood or a lack of interest or pleasure in things that were usually enjoyed as well as changes in eating and sleep habits, changes in motor activity, feelings of worthlessness and guilt, lack of concentration, and suicidal ideation or behavior being experienced) for a duration of at least one week. These symptoms had to cause severe impairment in functioning and could not be due to a substance or a general medical condition.[29] Finally, for a hypomanic episode, individuals had to experience at least four days of elevated, expansive, or irritable mood accompanied by the same manic symptoms noted previously. These symptoms could not be due to a substance or a general medical condition.[29]

Then, based on the mood episodes that were identified, diagnoses of bipolar I disorder, bipolar II disorder, and cyclothymia as well as bipolar disorder not otherwise specified could be made.[29] To receive a diagnosis of bipolar I disorder, individuals had to experience one or more manic or mixed episodes.[29] To receive a diagnosis of bipolar II disorder, individuals had to experience one or more depressive episodes and one or more hypomanic episodes (but no manic or mixed episodes). In the case of both bipolar I and bipolar II diagnoses, the episodes that were present could not be better accounted for by other diagnoses, and the symptoms had to cause clinically significant distress or impairment.[29] Further, to receive a diagnosis of cyclothymia, individuals had to experience numerous periods of hypomanic symptoms and numerous periods of depressive symptoms, such that there were no symptom-free periods that occurred for longer than two months at a time. Time frames varied for cyclothymia, with adults needing to exhibit this pattern for at least two years and children needing to exhibit this pattern for at least one year.[29] Finally, the category of bipolar disorder not otherwise specified was used when bipolar symptoms were experienced but did not fall clearly within any of the other categories listed here.[29]

Bipolar Disorder Symptoms in the *DSM-5*

With the *DSM-5*'s release in May 2013, it now can be noted that the bipolar disorder diagnostic criteria look similar to those listed in the *DSM-IV-TR.*[30] In the *DSM-5*, depressive, manic, and hypomanic episodes are identified using similar criteria to those

described above. In contrast, symptoms of mixed episodes now are replaced with a mixed features specifier (a specifier that can be used with any of the mood episodes.[32] This specifier is used when individuals experience full criteria for a manic episode and three symptoms of a depressive episode or when individuals experience full criteria for a depressive episode and three symptoms of a manic episode. This adaptation (i.e., the mixed features specifier) may allow for easier diagnosis in children.

With regard to the diagnoses themselves, the *DSM-5* again includes bipolar I disorder, bipolar II disorder, and cyclothymia. **As in the *DSM-IV-TR*, individuals have to experience one or more manic episodes to receive a bipolar I disorder diagnosis, and individuals have to experience one or more depressive episodes and one or more hypomanic episodes (but not any manic episodes) to receive a bipolar II disorder diagnosis.**[30] **In addition to these traditional diagnoses, there are listings for substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder,**[30] **allowing for more latitude in making an appropriate diagnosis.**

Other Bipolar-Related Symptoms that May Be of Relevance for Children

At this point, it should be clear that researchers have identified the experience of bipolar disorder in children and that *DSM* criteria are being used to make bipolar disorder diagnoses in children. **Nonetheless, bipolar disorder still is considered to be rare in children by many (e.g., see ref. 33), with some researchers reporting that many children are overlooked in the diagnosis of bipolar disorder due to a lack of clarity in the diagnostic criteria and concerns about the validity of this diagnosis in children.**[34,35] For example, although children in one sample of 36 consecutively hospitalized preschool children who were 3 to 5 years of age exhibited an irritable mood, evidenced a strong family history of affective illness, and had exhibited previous symptoms of ADHD, only 17% were diagnosed with bipolar disorder.[36] Further, given that some developmental differences in the manifestation of adult-onset versus childhood-onset bipolar disorder were identified (e.g., with children showing more mixed symptoms,[37,38] many children may be assigned an incorrect diagnosis. Such difficulties in diagnosis may be particularly problematic, as accurate diagnosis is critical for avoiding mislabeling and unnecessary medication exposure.[39] In fact, a diagnosis of bipolar disorder not otherwise specified often may serve as a default, particularly when children may not exhibit a full constellation of symptoms or meet the prescribed symptom duration criterion.[38,40]

Nonetheless, the course of bipolar disorder symptoms in children hopefully will become clearer as more researchers begin to examine this issue. For example, Birmaher and colleagues[41] examined the four-year longitudinal course of bipolar symptoms in children and adolescents who ranged in age from 7 to 17 years and who had some constellation of bipolar symptoms. In this study, bipolar disorder not otherwise specified was diagnosed if a child exhibited clinically relevant bipolar symptoms that did not meet criteria for bipolar I disorder or bipolar II disorder.[42] Based on their findings, the majority of children who had been diagnosed with a bipolar spectrum disorder (81.5%) experienced a complete recovery from their symptoms by 2.5 years following their index episode, although 62.5% of these children experienced a recurrence of syndromal symptoms within an additional 1.5 year time period. The majority of these children with recurring symptoms experienced depressive symptoms or mixed presentations, with a much lower frequency of manic symptoms. A number of children moved from bipolar disorder not otherwise specified to bipolar I disorder or bipolar II disorder (38%) and from bipolar II disorder to bipolar I disorder (25%).[41] **In addition to examining the course of bipolar disorder symptoms in this study, Birmaher and colleagues**[41] **identified several predictors of poorer outcomes, including an early onset of symptoms, a diagnosis of bipolar disorder not otherwise specified, a long duration of illness, a family history of mood disorders, and low socioeconomic status.**

Given these considerations, it certainly may be challenging to identify bipolar disorder (as well as prodromes and early markers of the disorder) in children. Given

the difficulties that children (particularly preschool children) face in verbalizing their emotions[42] and in recognizing and describing their own behaviors, researchers often may have to rely on the report of parents[33] or other informants and should look to evidence-based assessment recommendations.[39] Making distinctions between clinically significant symptoms and nonclinical behaviors still may be difficult, however. For example, distinguishing fantasies about special powers from clinically concerning levels of grandiosity and determining the cutoff for the frequency and/or intensity of euphoric states that should be of clinical concern may be more difficult in children (particularly preschool children).[2,39] Nonetheless, research suggested that children as young as 3 years of age can manifest manic symptoms, with many parents claiming that these symptoms always had been present.[33,35,43] Given the relative certainty that bipolar *symptoms* do occur in children, further information beyond that provided in the *DSM* may be helpful.

Bipolar Phenotypes:

Although formal diagnostic criteria are available, the *National Institute of Mental Health* (NIMH) organized a *Roundtable on Prepubertal Bipolar Disorder in Children* in 2000[44] to provide further clarity regarding bipolar symptoms in children. By this time, there were at least a dozen different research groups investigating bipolar symptoms in children.[45] Participants in this roundtable agreed that the *Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)* should be used to diagnose childhood-onset bipolar disorder, that children could present with *broad* or *narrow* phenotypes of bipolar disorder, and that bipolar disorder in children was highly comorbid with ADHD and other behavior disorders. A major issue that remained unresolved, however, was the assessment of mood variability and its convergence with bipolar I disorder, bipolar disorder not otherwise specified, and other disorders entirely.[45]

Nonetheless, this roundtable prompted further research. One of the lines of thinking that came from this roundtable was that of Leibenluft and colleagues,[46] who described a more uniform terminology for describing bipolar phenotypes, suggesting that childhood-onset bipolar disorder should be defined with several subtypes. These subtypes included the *narrow* subtype (for those who exhibited distinct mood episodes with hypomania or mania and elevated mood or grandiosity, with these episodes being more narrowly defined but less researched than those in the *DSM*), two *intermediate* subtypes (for those who exhibited clear episodes with hallmark *DSM* symptoms of hypomania or mania but who did not meet the duration criteria for these episodes and for those who exhibited irritable but not elevated mood), and the *broad* subtype (for those who exhibited chronic, nonepisodic symptoms of irritability and hyperarousal). Other researchers developed different rubrics. For example, Geller and Luby[47] suggested that childhood-onset bipolar disorder manifested with chronic, nonepisodic, rapid cycling, mixed manic states could cooccur with ADHD and conduct disorder. Further, they required euphoric mood and grandiosity to be present. Further, Wozniak and colleagues[48] emphasized that severe irritability was the predominant mood state and that grandiosity was not overrepresented in childhood-onset bipolar disorder. Thus, although much work ensued regarding potentially helpful descriptions of bipolar symptoms, there is still little consensus.

Duration of Manic Symptoms:

Although there are different symptom rubrics that may be used to identify bipolar symptoms in children, researchers also noted that the duration of bipolar symptoms should be considered carefully. **Although children may meet the *DSM* symptom criteria for bipolar disorder or be described in a meaningful fashion using one of the rubrics noted above, one of the leading reasons that children may not be diagnosed with bipolar disorder is because they do not meet the stringent *DSM* duration criteria for hypomania and mania.**[29,37,42,49,50] This issue with the duration of criteria can occur with adults as well (e.g., see ref. 51). Nonetheless, children often seem to exhibit a very rapid fluctuation in mood symptoms, especially when such symptoms are comorbid with other disorders.[42]

To better classify these symptoms based on duration, Suppes and colleagues[52] modified Kramlinger and Post's[53] definitions of rapid cycling. In particular, they defined rapid cycling as the experience of more than four mood episodes per year, ultrarapid cycling as the experience of more than four episodes per month, and ultraradian cycling as the experience of more than one mood episode per day for at least four days per week.[54]

Generally, the *International Society for Bipolar Disorders* (ISBD) Task Force found support for the current definition of rapid cycling.[55] Recent research also supported the presence of ultrarapid and ultraradian cycling in children;[50,54] however, the *ISBD* Task Force suggested that a dimensional approach to ultrarapid cycling and to the boundary between ultrarapid cycling and mixed episodes may be warranted.[55] Further, Leibenluft and colleagues[46] suggested that an episode theoretically can last only a few hours but that such episodes often are underresearched given the difficulties of examining a span of hours rather than days or weeks. In the context of such findings, Axelson and colleagues[49] proposed that the duration criteria for manic and hypomanic episodes may not be appropriate for children. Nonetheless, use of common definitions of remission for such episodes (e.g., at least four weeks with no more than two depressive or manic symptoms)[56] may be helpful. Thus, the duration and the frequency of mood states should be examined carefully in children.

Neurobiology of Bipolar Disorder:

Although neuroimaging studies have fostered some understanding of the pathophysiology of bipolar disorder in adults (albeit with this understanding being based on mixed results from adult studies), less is known about the pathophysiology of bipolar disorder in children. Based on the research that is being done currently, it seemed that there are several target brain areas that have been gaining support in making a contribution to bipolar symptoms in children and adolescents. Similar to adult studies that have suggested a role of subcortical structures in bipolar disorder (e.g., see ref. 57), research suggested that children and adolescents with familial bipolar disorder have smaller volumes in their amygdala relative to those of control children and adolescents.[58-60] Although some studies suggested that children with bipolar disorder do exhibit differences in the volumes of the hippocampus, caudate, or thalamus relative to healthy controls,[59] other studies suggested that smaller volume in the amygdala can be accompanied by smaller volume in the hippocampus in children with bipolar disorder.[58] Chang and colleagues[59] also noted that there is a relationship between past use of lithium and valproate and greater gray matter volume in the amygdala.

Other studies also suggested that children and adolescents with familial bipolar disorder may have underlying abnormalities in the regulation of prefrontal-subcortical circuits. For example, Chang and colleagues[61] found that children and adolescents with familial bipolar disorder have greater activation in their bilateral anterior cingulate cortex, left putamen, left thalamus, left dorsolateral prefrontal cortex, and right inferior frontal gyrus during a visuospatial working memory task, whereas children and adolescents in the control group have greater activation in their cerebellar vermis. Other studies also reported that children and adolescents who experienced at least one manic or hypomanic episode have reduced gray matter volume in the left dorsolateral prefrontal cortex, the left accumbens, and the left amygdala (e.g., see ref. 62) and that adolescents with bipolar disorder have decreased volume in the left superior temporal gyrus.[63] Overall, the role of the bilateral anterior cingulated cortex and the dorsolateral prefrontal cortex are not unexpected, given their suspected role in normal mood regulation (e.g., see ref. 64) and in attention (e.g., see ref. 65). More work is needed, however, to clarify the neurobiology of bipolar disorder in children and adolescents.

Comorbid Diagnoses:

In addition to issues with symptom duration, frequency of mood states, and neurobiology, the constellation of comorbid symptoms that occur in conjunction with bipolar disorder may require closer examination in children as well. Differential diagnosis may be difficult given that bipolar disorder and other diagnoses include symptoms that occur commonly in children (e.g., irritability). For example, when children present with abnormal mood, irritability, and hyperactivity, there can be substantial discrepancies across health service providers about which diagnosis may be most appropriate.[46] Discussions of differential diagnosis and comorbidity may be facilitated by returning to the four subtypes of childhood-onset bipolar disorder described by Leibenluft and colleagues.[46] As already noted, these subtypes were the narrow subtype, two intermediate subtypes (also depicted as mania-not otherwise specified (short episodes, hallmark symptoms) and irritable mania (full-duration episodes, no hallmark symptoms)), and the broad subtype.

As already noted (via ref. 46), the narrow subtype can be used to describe children who meet full *DSM-IV-TR* diagnostic criteria for mania, including the duration criteria and characteristic symptoms of mania (e.g., an elevated/expansive mood, an increase in goal-directed activity, and grandiosity).[29] With regard to the intermediate subtypes, the mania-not otherwise specified (short episodes, hallmark symptoms) phenotype characterizes children who experience mania episodes that are shorter than the prescribed duration but who meet the rest of the *DSM-IV-TR* diagnostic criteria for manic episodes. In contrast, the irritable mania (full duration episodes, no hallmark symptoms) phenotype can be used to describe children who exhibit irritability only, rather than elevated/expansive mood, and who meet the rest of the *DSM-IV-TR* diagnostic criteria for manic episodes. Finally, the broad subtype can be used to describe children who have a chronic, nonepisodic illness that does not meet criteria for manic episodes but who still exhibit symptoms of severe irritability and hyperarousal. According to Leibenluft and colleagues,[46] these children may never develop a classic mania presentation; however, they still may follow the clinical course of bipolar disorder. Recent research[66] suggested that this phenotype may be distinct from bipolar disorder (e.g., even having different predictors). These descriptions may better capture the symptoms exhibited by children in the context of bipolar disorder.

With these phenotypes in mind, it should be clear that children who have bipolar disorder can experience symptoms that overlap greatly with other childhood disorders.[67,68] Specifically, research proposed that many children with bipolar disorder also meet criteria for ADHD, major depression, anxiety disorders, ODD, other behavior disorders, and psychosis, even after overlapping symptoms (e.g., distractibility, motoric hyperactivity, and talkativeness) are removed.[33,43,69–74] Thus, those working with children should be aware of cooccurring diagnoses, particularly since some distinctions may be more difficult than others.

For example, classifying cooccurring hyperactivity and overaggressiveness may make the bipolar disorder diagnostic picture more difficult, as research suggested that the most common symptoms of bipolar disorder are "excessive energy, decreased need for sleep, impairing elation, and hypersexuality" as well as aggression and irritability.[46,74, p. 393;75] Thus, many researchers have been concerned with the overlap between bipolar disorder and ADHD[76, 77] and between bipolar disorder and ODD. In particular, Leibenluft and colleagues[46] suggested that many symptoms in bipolar disorder (e.g., talking excessively, impulsivity, having poor judgment, irritability, often running about or climbing excessively, and distractibility) lack specificity to bipolar disorder and also are present in ADHD.[40,43,73,75] **Further, for those researchers who suggested that mania can be chronic (a minority viewpoint), it may be difficult to differentiate bipolar disorder and ADHD if health service providers are looking for specific episodes or mood swings.[43]**

Nonetheless, Wozniak and colleagues'[43] study provided wider recognition to the similarity between ADHD and childhood-onset bipolar disorder. They claimed that the children with ADHD in their study who exhibited anger, oppositionality, and hyperactive behavior also met *DSM* criteria for childhood-onset bipolar disorder. They recommended that more research be conducted to determine if these children had ADHD, bipolar disorder, or both. In addition, Luby and colleagues[74] found that it was challenging for clinicians to differentiate oppositional behaviors (often found in ODD) from the grandiosity and euphoric mood that is experienced with bipolar disorder (e.g., see ref. 75). As a result, they proposed that health service providers should determine whether the oppositional behaviors are generalized or relationship specific to assist in making a distinction.

Beyond ADHD and ODD, Luby and Belden[35] also suggested that preschoolers with bipolar disorder experienced a greater severity of depression and more comorbidity than those preschoolers with major depressive disorder. Nonetheless, many of these symptoms also were present in other psychiatric disorders, making differential diagnosis difficult.[40,73] More recently, in order to better distinguish affective and behavioral disorders first seen in childhood, APA proposed a new diagnostic category, disruptive mood dysregulation disorder (DMDD, previously known as severe mood dysregulation and temper dysregulation disorder, e.g., see ref. 66), for *DSM-5*.[30] DMDD is described as a disorder that is characterized

by extreme, recurrent temper outbursts (both physical and verbal) that are disproportionate to the provocation or stressor prompting the outburst and inconsistent with children's developmental level.[30] DMDD is proving to be a controversial addition to the *DSM-5*, with some researchers voicing significant reservations about this disorder (e.g., see ref. 78). Given its reference to dysregulation of mood and emotion, however, this disorder may aid in the facilitation of research on the causes, features, and treatment of childhood-onset bipolar disorder as researchers continue to try to differentiate one disorder from the other given that bipolar disorder is proving to be a disorder that is distinct from DMDD (e.g., see ref. 66).

Nonetheless, childhood-onset bipolar disorder now is recognized and does share features with adult-onset bipolar disorder. For example, researchers suggested that there is continuity in symptoms across adolescence[41] and into adulthood.[79] Further support for the continuity of symptoms over the course of development was supported by family studies comparing children with bipolar disorder to their parents who had bipolar disorder via neuroimaging[61] and with genetic studies.[80] Findings in these studies suggested that bipolar disorder with an onset in childhood may be genetically loaded and homogenous,[80] allowing for the documentation of similarities across family members.

Given the challenges that are present when identifying and diagnosing bipolar disorder in children (particularly preschool children), it may prove beneficial to consider Robins and Guze's[81] research validation paradigm for identifying a valid syndrome (e.g., see ref. 37, 46, 82, 83). They proposed that a syndrome should have a reliable clinical description, consistent support from research studies, differentiation from other clinical disorders, evidence from follow-up research indicating that clinical outcomes of patients are similar or do not meet criteria for another disorder, and proof of increased prevalence rates in family studies. **Although specific considerations that are necessary for the diagnosis of bipolar disorder in children are not completely clear (beyond actual *DSM* criteria), the fact that these children experience significant impairment in family, school, and social functioning should be emphasized. In addition, these children exhibit poor global functioning, utilize mental health care facilities, and attempt suicide more frequently,[34] suggesting the severity of their symptom presentation.**

With this information in mind, more specificity and sensitivity could be achieved for bipolar disorder diagnoses in children. For example, a meta-analysis conducted by Kowatch and colleagues[73] suggested that the most frequently occurring symptoms of mania in children include increased energy, distractibility, and pressured speech, with 89%, 84%, and 82% of children displaying these symptoms, respectively. Additionally, 78% of children experienced grandiosity, 72% of children experienced decreased need for sleep, 70% of children experienced elation/euphoria, and 69% of children exemplified poor judgment. In contrast, the rarest symptoms experienced by children with bipolar disorder were flight of ideas (56%) and hypersexuality (38%).[73] Other research suggested that about one-fifth of children with bipolar disorder experience delusions or hallucinations during a mood episode. Further, psychosis was more common among children meeting criteria for bipolar disorder than among children with ADHD.[40, 69, 84] Based on these findings, particular specific symptoms also may prove to be distinguishing factors when making a bipolar disorder diagnosis in children.

Irritability:

One symptom that may deserve more consideration than others when attempting to understand bipolar symptoms in children is irritability, emphasizing an important component of the *DSM-IV-TR* bipolar criterion of "a distinct period of abnormally elevated, expansive, or irritable mood."[29, 68] In fact, the rationale for the intermediate subtypes described above was that irritability is not pathognomonic to bipolar disorder but rather is ubiquitous in childhood psychopathology[46,66,69,75] and also can occur in typically developing children). For example, irritability may be present in at least six childhood disorders (e.g., major depressive disorder, generalized anxiety disorder, posttraumatic stress disorder, ADHD, ODD, conduct disorder.[68, 85] As a result, it will be important to determine whether children's irritability is part of bipolar disorder or some other disorders.[85, 86]

Clearly, some research suggested that irritability is an important marker in childhood-onset bipolar

disorder as it may be a sign of severity (e.g., see ref. 87). For example, Biederman and colleagues[69] suggested that irritability in children with bipolar disorder is "very severe, persistent, and highly disabling, and often associated with violence" (p. 54). Further, in their meta-analysis, Kowatch and colleagues[73] suggested that 81% of children with bipolar disorder experienced irritability. Nonetheless, given that no *DSM* diagnosis captures the symptomatology of predominantly severe, nonepisodic irritability well, more attention is needed in classifying this symptom.[68] In particular, for symptoms of irritability to be useful in making a diagnosis, definitions of irritability that account for the context in which it occurs and its episodicity and chronicity would be required. Currently, the *DSM* does not define irritability, making it difficult for health service providers to clearly identify this symptom in children[29,30,66,68,88] Other definitions do exist in the literature, however. For example, the *K-SADS*[89] defined irritability as "anger, crankiness, bad or short tempered, resentment or annoyance, touchy or easily annoyed."[88, p.410] Further, the *Diagnostic Interview Schedule for Children* (*DISC*; see ref. 90]) defined irritability as "cranky, angry toward people you had no reason to, talking back, or temper tantrums."[62, p.410] The *Children's Depression Rating Scale*[91] also defined irritability as "grumpy, crabby, talked back, sassy, wouldn't do something your parents asked you to do."[62, p.410] Nonetheless, it is difficult to identify this symptom with any degree of certainty.[62]

Others emphasized the importance of irritability in establishing bipolar disorder diagnoses in a manner more consistent with the suggestions of Wozniak and colleagues.[43] In such cases, a diagnosis would be recommended if children meet *DSM* criteria with irritability as a core symptom and without the presence of elation, grandiosity, and episodicity. Nonetheless, some research suggested that there may not be many differences between those children who exhibit episodic irritability versus those who exhibit episodic elation. In particular, a study by Hunt and colleagues[92] noted that these two groups of children do not differ in their rate of psychiatric comorbidities, severity or duration of illness, or family history of mania. The main difference between these two groups was that children who exhibit irritability have more symptoms of depression and alcohol abuse and that children who exhibit elation have more manic symptoms. Still others used some combination of these recommendations by considering irritability to be a core symptom only if it is accompanied by elated mood or grandiosity.[46] Given these inconsistencies, research is needed to provide further clarity regarding the relative importance of irritability, grandiosity, and elation in making a diagnosis of bipolar disorder in children.[93]

Emotion Regulation:

Although not yet examined widely in the context of bipolar disorder in children, emotion (dys)regulation also may prove helpful in delineating the bipolar symptoms that children are experiencing (e.g., see 94; see ref. 95, for a review; see ref. 96, for further information). **Those who are diagnosed with bipolar disorder obviously experience difficulties in their emotion regulation.**[33,97,98] This is true especially for preschool children, a population that recently received much attention and debate concerning the diagnosis of bipolar disorder.[33,46,74,88,98-101] For example, despite the key differences between the subtypes of childhood-onset bipolar disorder proposed by Leibenluft and colleagues,[46] the children in each of these subtypes still experience a shared impairment in emotion regulation.[33,99] As a result, emotional dysregulation may be viewed as an important characteristic of bipolar disorder,[46] while also considering the changes in energy[30] and cognitive disruptions[102] that can accompany a bipolar disorder presentation.

Although Leibenluft and colleagues[46] conceptualized childhood-onset bipolar disorder as having phenotypes, these phenotypes also can be viewed as being on a spectrum (similar to the spectrum that now is used for pervasive developmental disorders; also see ref. 103). Located at one end of the bipolar spectrum is the narrow subtype, as it is characterized by the classic manic and depressive symptoms usually manifested in adults. On the other extreme of the bipolar spectrum lies the broad subtype, characterized by highly impairing, chronic, and nonepisodic irritability.[66] Such a bipolar spectrum would suggest that bipolar disorder consists of varying degrees, severities, and presentations of emotional dysregulation and other symptoms. Generally, it is advantageous for health service providers to use a bipolar spectrum with children because a group of specific categorical bipolar

diagnoses may not encompass all of the children needing treatment for bipolar symptoms, especially if they do not fit exact criteria. Thus, although emotion regulation is not addressed or included explicitly in the *DSM-5*, it may prove beneficial to examine emotion regulation when considering a diagnosis of bipolar disorder in children.[29, 66] Nonetheless, Luby and Belden[33] indicated that emotion regulation is difficult to operationalize and quantify.

Thus, in order to discuss emotion regulation in the context of bipolar disorder in children, a definition would be needed. In its most basic sense, emotion regulation involves individuals' ability to control their reactions, affect, emotions, and mood.[33,97,99] Further, Dickstein and Leibenluft[99] explained in greater detail that emotion regulation consists of three major processes, including being able to detect a stimulus in the environment, to generate an emotional response, and to process or control emotion. When stated simply, it becomes evident that children who have a disorder on the bipolar spectrum experience emotional dysregulation, as evidenced by their increased emotional lability, intensity, and reactivity.[74] Other researchers discussed emotion regulation from a neurobiological perspective, however. For example, the prefrontal regions of the brain play an inhibitory role in emotion regulation, whereas subcortical regions (that encode and represent information about emotions) experience decreased activation (e.g., see 97). Alloy and Abramson[104] also suggested that a *behavioral approach system* (BAS) dysregulation theory may further the understanding of the psychosocial and biological features of bipolar disorder, with the lability in mood, energy, motivation, cognition, and activity that is experienced being associated with high BAS sensitivity (in contrast to the effects of an individual being overregulated). Researchers noted, however, that much controversy still surrounds the topic of emotion regulation, as there has not been unanimous agreement on its exact definition or its proper measurement and assessment.[33, 99]

To further complicate matters, emotional dysregulation is part of typical childhood development and is present in all children at certain points in time. Nonetheless, emotional dysregulation becomes indicative of a disorder when it clearly is impairing to children's functioning, is developmentally inappropriate for children's age, and is inappropriate or out of proportion relative to the situational or environmental triggers that children are experiencing.[74, 88] Once emotional dysregulation is considered in terms of this developmental context, it may become a useful consideration in the context of bipolar disorder in children. In fact, Luby and Belden[33] suggested that there are actually two forms of emotional dysregulation that may be important for childhood-onset bipolar disorder. The first form of dysregulation can be described as *underregulation* and is evident when children are unable to regulate their emotions enough. In this form of dysregulation, emotions become out of control. Emotional underregulation also is related to *behavioral disinhibition*, where children experience difficulties in controlling and modifying their inappropriate behaviors and experience impulsivity, absence of restraint, high approach, and disinhibited behaviors and speech in novel situations. Emotional underregulation and behavioral disinhibition may lead to externalizing problems in children, even in young children.[33, 100, 101] Conversely, the second form of emotional dysregulation can be described as *overregulation* and is evident when children regulate their emotions too much. As a result, their emotions are dulled or dampened.[33] Luby and Belden[33] suggested that emotional overregulation also is related to *behavioral inhibition* and may lead to internalizing problems in children, even in young children.[33, 100] Overall, Hirshfeld-Becker and colleagues[100] suggested that examining the overlap and relationship between emotion regulation and behavioral inhibition and disinhibition should prove to be a productive area of research in the future.

Certainly, discussing the effects of both emotional underregulation and overregulation brings to mind the hallmark features of bipolar disorder in children. Bipolar disorder is characterized by both highs (mania) and lows (depression), often exhibited by children as externalizing and internalizing behaviors, respectively.[29, 33, 74] Luby and Belden[33] conceptualized childhood-onset bipolar disorder as the combination of emotional underregulation and overregulation contributing to such problematic behaviors. They suggested that externalizing problems in children (particularly young children) result from

the underregulation of negatively valenced emotions (e.g., anger) and affect. Additionally, they proposed that internalizing problems in children (particularly young children) may be caused by a constellation of emotional regulatory and behavioral difficulties, including children's overregulation of positively valenced emotions (e.g., joy), underregulation of negatively valenced emotions (e.g., sadness), and inhibited behavioral ability to generate feelings of pleasure.[33] The simultaneous presentation of such externalizing and internalizing behaviors can be indicative of rapid cycling and mixed episodes, both of which are thought to be more common in children.[93, 99] Emotional dysregulation also may be used to explain more classic manifestations of bipolar disorder in children, however. For example, children may underregulate positively valenced emotions (e.g., happiness), resulting in elation or the elevated/expansive mood characteristic of mania in adults.[33]

Although research is beginning to consider emotional dysregulation as a symptom of childhood-onset bipolar disorder, emotional dysregulation also may be a prominent feature of many other childhood disorders (e.g., ADHD, ODD, CD). Therefore, health service providers still must use caution when examining children whom they suspect may lie on the bipolar spectrum due to difficulties with emotion regulation. The symptom of emotional dysregulation alone is, of course, not enough to diagnose children with bipolar disorder (or any other disorder, for that matter). Several researchers suggested, however, that emotional dysregulation and behavioral disinhibition are likely early markers for bipolar disorder.[98, 101] Although a diagnosis cannot be made based only upon the presence of an early marker or prodrome, such evidence may allow health service providers to observe closely those children who may be most likely to be at risk due to emotional dysregulation and to monitor them for the later bipolar symptoms. Such monitoring also will allow researchers to conduct longitudinal studies in the area of emotional dysregulation and bipolar symptoms.

To provide a further narrowing of focus, emotional reactivity may be a particularly important component of emotional dysregulation. In fact, children with bipolar disorder appear to experience difficulties with increased emotional reactivity. For example, Chang and colleagues[105] suggested that children who are at risk for developing bipolar disorder experience difficulties in reactivity. They found that children of parents who have bipolar disorder showed difficulties with emotional reactivity by continuing to exhibit anger or depression despite being consoled by another individual.[105] Further, based on parent reports, Luby and colleagues[74] discovered increased emotional reactivity in children with bipolar disorder as well. For example, they found that, after a joy-inducing stimulus event, preschoolers who were diagnosed with bipolar disorder expressed significantly higher levels of joy than typically developing peers at 30 and 60 minutes after the event. These preschoolers retained these significantly higher levels of joy at lunchtime and at dinnertime. Preschoolers with bipolar disorder also expressed significantly higher levels of sadness after a sadness-inducing event at 30 minutes after the event. Further, these preschoolers expressed significantly higher levels of anger initially and 30 minutes after an anger-inducing event.[74] Such findings were consistent with those of Gruber et al.,[106] who found that interepisode bipolar disorder in adults was related to greater rumination about positive and negative emotions and that this rumination was related to illness course.

Luby and colleagues'[74] study also elicited some intriguing results that may help researchers and clinicians differentiate between preschoolers with bipolar disorder and preschoolers with other disruptive behavior disorders. Preschoolers with bipolar disorder expressed significantly higher levels of joy than disruptive preschoolers at 30 and 60 minutes after a joy-inducing event and at lunchtime. Preschoolers with bipolar disorder also expressed significantly higher levels of sadness 30 minutes and 60 minutes after an event inducing that feeling and at bedtime. Additionally, preschoolers with bipolar disorder expressed significantly higher levels of initial anger and anger at 30 minutes and 60 minutes after an event inducing this emotion.[74] This evidence demonstrated that young children with bipolar disorder experience difficulty with emotion regulation and intensity over long periods of time. These differences in reactions pointed to the increased emotional reactivity

and intensity displayed by young children with bipolar disorder but not with other disruptive behaviors. Thus, observations of emotional reactivity may aid in complex differential diagnosis[74] although it also should be recognized that emotional regulation is not specific to bipolar disorder and may prove to be important to other diagnoses as well (e.g., see ref. 107).

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

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Multiple-Choice Questions

13. According to the lesson, research indicates that mania is often overlooked in children because:

A. children do not manifest bipolar symptoms until adulthood.

B. manic symptoms in children often overlap with symptoms of other disorders.

C. there was no documented research prior to the 1970s that studied bipolar symptoms in children.

D. All of the above

14. Bipolar disorder diagnostic criteria in the DSM-5:

A. lists symptoms of mixed episodes with a mixed feature specifier that can be used with any of the mood episodes.

B. are significantly different than those listed in the DSM-IV-TR.

C. lists symptoms that cannot be due to a general medical condition.

D. All of the above

15. Birmaher and colleagues identified several predictors of poorer outcomes in the course of studying bipolar symptoms in children which include:

A. late onset of symptoms.

B. high economic status.

C. a diagnosis of bipolar disorder not otherwise specified

D. a short duration of illness.

16. Concerning the diagnosis of bipolar disorder in children, according to the lesson:

A. children are often overlooked due to the lack of clarity in the diagnostic criteria.

B. children may not meet the stringent DSM duration criteria for hypomania and mania.

C. children who have bipolar disorder often experience symptoms that overlap with other childhood disorders such as ADHD, major depression, anxiety disorders and ODD.

D. All of the above

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Best Practices in CME

Bipolar Disorder in Children, Part 1: An Overview

By Kimberly Renk, PhD; Rachel White; Brea-Anne Lauer; Meagan McSwiggan; Jayme Puff; and Amanda Lowell

ID#: L003346

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

CME Lesson Overview

This lesson aims to assist health service providers glean a snapshot of the literature in this area so that they can gain an understanding of diagnostic criteria and other behaviors that may be relevant. Clinicians will be informed about potential approaches for assessment and treatment of children who meet bipolar disorder criteria.

Key Point 1: Background

Although bipolar disorder historically was thought to only occur rarely in children and adolescents, there has been a significant increase in children and adolescents who are receiving this diagnosis.

Key Point 2: Diagnostic Criteria in the DSM-IV and DSM-IV-TR

The criteria for bipolar disorder as described in the *DSM-IV* and *DSM-IV-TR* were used to diagnose bipolar disorder which is listed as a mood disorder. A manic episode was identified when an individual experienced a constellation of symptoms for a specified duration of time. For a mixed episode, individuals had to experience symptoms consistent with both a manic episode and a depressive episode for a duration of one week. The symptoms in both manuals cannot be due to a substance or a general medical condition.

Key Point 3: Diagnostic Criteria in the DSM-5

To further classify symptoms, the DSM-5 has replaced symptoms of mixed episodes with a mixed features specifier: a specifier that can be used with any of the mood episodes. This specifier is used when individuals experience full criteria for a manic episode and three symptoms of a depressive episode or when individuals experience full criteria for a depressive episode and three symptoms of a manic episode. Further, there are listings for substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder.

Key Point 4: Symptom Overlap

Children who have bipolar disorder often experience symptoms that overlap with other childhood disorders such as ADHD, major depression, anxiety disorders and ODD; therefore clinicians should be aware of co-occurring diagnoses.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Bipolar Disorder in Children, Part 2: Assessment and Interventions

Kimberly Renk, PhD; Rachel White; Brea-Anne Lauer; Meagan McSwiggan; Jayme Puff; and Amanda Lowell

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

KEY WORDS: Bipolar Disorder • DSM-5 • Assessment • Mania • Pharmacotherapy • CBT

LEARNING OBJECTIVES: This lesson reviews recommendations for assessing bipolar disorder in children. Clinicians will also review psychosocial and medication treatment interventions when managing bipolar disorder alone as well as with comorbid psychiatric disorders.

ABSTRACT: Although bipolar disorder historically was thought to only occur rarely in children and adolescents, there has been a significant increase in children and adolescents who are receiving this diagnosis more recently (Carlson, 2005). Nonetheless, the applicability of the current bipolar disorder diagnostic criteria for children, particularly preschool children, remains unclear, even though much work has been focused on this area. As a result, more work needs to be done to further the understanding of bipolar symptoms in children. It is hoped that this paper can assist psychologists and other health service providers in gleaning a snapshot of the literature in this area so that they can gain an understanding of the diagnostic criteria and other behaviors that may be relevant and be informed about potential approaches for assessment and treatment with children who meet bipolar disorder criteria. First, the history of bipolar symptoms and current diagnostic criteria will be discussed. Next, assessment strategies that may prove helpful for identifying bipolar disorder will be discussed. Then, treatments that may have relevance to children and their families will be discussed. Finally, conclusions regarding work with children who may have a bipolar disorder diagnosis will be offered.

COMPETENCY STATEMENT: This lesson will help clinicians gain an understanding of assessing bipolar disorder symptoms in children. Children presenting with bipolar symptoms often present with overlapping symptoms of other comorbid childhood psychiatric disorders. Upon completion of this lesson, clinicians will be better equipped to consider the similarities in the assessment of these symptoms as well make treatment recommendations utilizing medication and psychotherapy.

Valuable Perspectives on Assessment

Given the nature of the symptoms that are displayed by children struggling with bipolar symptoms, the commonality of certain symptoms across different disorders (e.g., bipolar disorder versus ADHD), and the need for more attention regarding other characteristics that potentially may be helpful in making a bipolar disorder diagnosis (e.g., irritability, emotional dysregulation), the assessment of bipolar disorder in children likely will be challenging. The purpose of this section is to highlight basic guidelines for assessing bipolar disorder in children. As a means of assisting with the assessment of bipolar symptoms, AACAP[108] published a Practice Parameter in 2007 for assessing bipolar disorder in children. Specifically, four recommendations were provided for the assessment of bipolar disorder in children. The first recommendation suggested that *DSM* criteria should be followed when diagnosing mania or hypomania.[108] Because symptoms such as irritability and emotional lability are seen across many disorders of childhood and also can be seen in typically developing children, adhering closely to the operational definitions of mania and hypomania provided in the *DSM* may foster a clearer diagnostic picture for children. In particular, close attention to the pattern and duration of bipolar symptoms and how these symptoms relate to sleep, motor activity, and changes in cognitive functioning can provide key information that health service providers can use to parse out the likelihood that such symptoms may be due to bipolar disorder or some other disorders.[108]

The second recommendation in the Practice Parameter[108] was that bipolar disorder not otherwise specified should be used for children who display an atypical duration of bipolar symptoms. Given that the course of symptoms in children can vary greatly relative to *DSM* criteria and that interventions for bipolar disorder in children resemble those provided to adults (although there is still uncertainty regarding the effectiveness and safety of using such an adult-oriented approach), this recommendation may facilitate children receiving interventions that may prove useful in alleviating the bipolar symptoms that they are experiencing. The Practice Parameter further reported that children who are diagnosed with bipolar disorder not otherwise specified have high rates of comorbid disorders, both in the internalizing and externalizing domains, and that the moods of these children are generally volatile and reactive.[108] As a result, this recommendation implies that health service providers must understand clearly other factors (e.g., situational triggers, reinforcement of outbursts, communication difficulties, and risk factors) that can facilitate the differential diagnosis of bipolar disorder versus other disorders (e.g., ADHD) and assist in identifying other comorbid diagnoses as well.

The third recommendation provided by the Practice Parameter[108] suggested that problems associated with bipolar disorder need to be assessed closely. These problems included suicidality, commonly comorbid disorders, psychosocial stressors, and medical problems. As a result, a comprehensive assessment that includes a thorough understanding of children's developmental abilities, cognitive functioning, and speech and language abilities (all of which may be particularly important for children, particularly preschool children) is warranted when assessing bipolar disorder. Such information also will facilitate a comprehensive treatment plan.

The final recommendation provided by the Practice Parameter[108] was that the diagnosis of bipolar disorder should be used cautiously in young children. The Practice Parameter underscored that the "diagnostic validity of bipolar disorder in young children has yet to be established."[108, p. 115] Children who present with mood and behavior problems may be experiencing various environmental and biological factors that may account for such problems (e.g., developmental delays, psychosocial stressors, parent-child relationship problems, and children's own temperament.)[108] Given that pharmacological interventions are the standard for bipolar disorder and given the lack of research on the safety and efficacy of such interventions for children, this diagnosis and consequent interventions should be considered carefully.

In addition to the recommendations offered as part of the Practice Parameter,[108] Baroni et al.[109] also provided detailed guidelines regarding the assessment of mania in children. Their recommendations suggested that both parents and children should be interviewed together and separately (when their age is appropriate to do so), that screening for mania should include questions about distinct periods of mood change and associated symptoms,

and that the period of time in which children display euphoria or heightened irritability should be identified. They also suggested that a developmental perspective should be used to evaluate the severity of the symptoms and whether they are clinically relevant, that it should be determined whether elation is comparable to or greater than positive affect during experiences that could cause great excitement (e.g., Christmas morning), that it should be determined whether manic symptoms occur during the mood change, and that grandiosity versus oppositionality should be considered by thinking about whether the behavior is a change from the norm and if it occurs along with other new symptoms. Lastly, they suggested that a distinction should be made between a decreased need for sleep and insomnia. Thus, many considerations for assessing bipolar disorder in children generally were offered.

Nonetheless, other considerations may be needed as well. Of particular importance for children, particularly preschool children, assessment should be an ongoing process in which children's symptoms are monitored over time.[110] In fact, children's behavioral history should be collected so that a baseline for behavior can be established (e.g., see ref. 110). This baseline will be important for understanding whether children's mood changes are significant. An important visual tool to consider in this process is a mood log, in which retrospective and prospective data about children's behaviors and symptoms can be tracked.[111] It also was recommended that, at the time of scheduling an assessment for a suspected bipolar disorder diagnosis, parents should be asked to log their children's symptoms for at least two weeks.[112] In this way, patterns of symptoms can be documented. Finally, practitioners should utilize multiple informants when possible,[111, 113] as multiple informants likely will provide useful information. Nonetheless, it will be particularly important to consider parents' reports, as this information may provide the best diagnostic accuracy.[113]

In addition, a detailed historical interview should be conducted, including symptom characteristics over time, responses to intervention, and familial psychiatric history. Such information can help health service providers further understand children's symptoms and whether these symptoms are truly indicative of bipolar disorder. **Family psychiatric history, in particular, is a well-established risk factor for bipolar disorder, with children of parents who have bipolar disorder being at five times higher risk for developing the disorder than other children.**[114, 115] Other important information for assessing bipolar disorder in children may include mood lability (e.g., rapid changes in episodic mood from manic to depressive symptoms versus the cooccurrence of depressive and manic symptoms), psychotic features that are mood contextual (e.g., delusions or hallucinations), and episodic aggressive behavior that is reactive in nature [116]. Such recommendations will better focus assessments of bipolar disorder in children.

Regarding specific assessment methods, other helpful papers exist detailing evidence-based methods (e.g., see ref. 39, 117) and specific assessment tools along with their psychometric properties (such as the *Kiddie Schedule of Affective Disorders and Schizophrenia* [KSADS], the *Diagnostic Interview Schedule for Children* [DISC], and the *Child Mania Rating Scales*; e.g., see ref. 111, 116, 117). Some brief examples will be overviewed here. Generally, structured or semistructured interviews are used to generate diagnoses for research (and sometimes for clinical) purposes. As listed above, the KSADS often is used for this purpose with parents of children and adolescents and sometimes with adolescents themselves. **Although the KSADS has sufficient coverage of bipolar symptoms,[118] administration of structured interviews can take a significant amount of time, resulting in a significant expense and a lack of feasibility for assessment situations.[119]**

As a result of these limitations of structured interviews, a variety of rating scales may be used instead. At times, more broad-based rating forms, such as the *Child Behavior Checklist* (CBCL, Achenbach and Rescorla,[120]) may be used, particularly as some suggested that the CBCL can be of assistance in identifying bipolar symptoms in children via the use of a constellation of its subscales (i.e., the attention problems, aggressive behavior, and anxious-depressed subscales).[121] **A potentially more useful and expedient option, however, may be to use scales that are created specifically to detect bipolar symptoms in children via ratings provided by parents (see ref.** 119**). There are several examples of such rating scales that have good psychometric properties, including the *Parent General Behavior Inventory***

(GBI),[113] the *Parent Young Mania Rating Scale* (YMRS [122]), and the *Child Bipolar Questionnaire* (CBQ).[119] Some studies suggested that specific parent rating scales, such as the GBI and the YMRS, produce fewer false alarms relative to broad-based scales, such as the CBCL.[110] Nonetheless, the GBI and the YMRS only assess manic and hypomanic symptoms, whereas the CBQ was developed to assess manic, depressive, and comorbid symptoms.[119] For the GBI and the YMRS, there are also self-report versions of these scales for children and adolescents; however, such scales may have more limited utility for younger children. Overall, the assessment of bipolar disorder should be both comprehensive and longitudinal in nature.[111]

Insights into Potential Therapeutic Interventions for Children

Once a thorough assessment has been completed, options for therapeutic intervention should be explored carefully. Although the literature on appropriate interventions for children with bipolar disorder is growing, more research is needed to further the understanding of which interventions will work best for which children. As a result, some of the options that are available for older children and adolescents are examined here in an effort to provide potential insight into those options that may prove efficacious for children, particularly preschool children, and to draw attention to the fact that more research is needed.

Medications:

Although psychopharmacological interventions may be considered most efficacious generally in the treatment of bipolar disorder, much of the available information regarding the efficacy of psychopharmacological interventions with childhood-onset bipolar disorder was extrapolated from the adult literature. As such, there were few studies that directly addressed the effects of these medications in children and adolescents.[38] There were even fewer studies that address the efficacy of these medications in preschool children with bipolar disorder. Generally, however, a theme in prescription recommendations was *primum non nocere* (i.e., first do no harm).[123] Nonetheless, it will be important to further investigate the long-term effects, efficacy, and side effects of these medications in children, particularly in preschool children.

With regard to the research available for children and adolescents generally, the most commonly prescribed medications for children and adolescents who exhibit bipolar symptoms were lithium, antiepileptic medications (i.e., divalproex sodium and carbamazepine), and atypical antipsychotic medications (i.e., risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole). Of these medications, lithium is approved by the FDA to treat mania in children who are 12 years of age and older, whereas risperidone and aripiprazole are approved for children who are 10 years of age and older.[124] Much of the research on children and adolescents indicated that, when used alone, these medications are relatively effective (see 124, 125), generally safe, and well tolerated.[126] Nonetheless, some suggested that atypical antipsychotics may be more effective than mood stabilizers (although they may promote more adverse events) when used in children and adolescents (e.g., see 127–129). For example, Geller and colleagues[128] reported that 279 children and adolescents who ranged in age from 6 to 15 years and who were diagnosed with bipolar I disorder had higher response rates to risperidone than to lithium and to divalproex sodium during the course of a controlled, randomized, no-patient choice, and eight-week protocol. Nonetheless, risperidone may promote serious metabolic effects.[128]

Beyond using one medication in an effort to treat bipolar symptoms, medications showed promising results when they were utilized in combination, whether that combination included multiple mood stabilizers[130] or mood stabilizers augmented with atypical antipsychotic medication.[126] For example, Findling and colleagues[131] indicated that children and adolescents who ranged in age from 5 to 17 years and who met criteria for bipolar I disorder or bipolar II disorder were treated safely and effectively using a combination of lithium and divalproex sodium. Once stabilized on this combination of medications, some children and adolescents could continue to be maintained and do well on either lithium or divalproex sodium; however, many children and adolescents experienced relapse or adverse events.[132] In order to effectively combine these medications, however,

multiple algorithms were proposed that systematically introduced both mood stabilizers and antipsychotics according to the individual needs of the children and adolescents and their respective treatment responses.[112, 133] Overall, preliminary results using this algorithm approach demonstrated success in reducing symptoms of childhood-onset bipolar disorder,[133] but, again, more research is needed on such approaches.

In the context of *primum non nocere*, it should be noted that, although these medications are used widely and are beneficial in treating bipolar symptoms, they often are accompanied by adverse side effects, including gastrointestinal distress (e.g., nausea, vomiting), headache, cognitive dulling, hypothyroidism, tremors, and extrapyramidal side effects.[112, 124, 134] Further, one particularly worrisome and common side effect is weight gain. Others also documented metabolic effects[135] and cardiovascular risks (although it is unclear if these risks may be present prior to the administration of medications).[136] Given such side effects, it was recommended that children and adolescents be monitored closely, particularly as these side effects can lead to a number of long-term effects.[112, 137] Further, such significant side effects also suggested that examination of alternative treatment options, such as flax seed oil and omega-3 fatty acids, is warranted.[138]

Often children and adolescents with bipolar symptoms also exhibited symptoms that were consistent with other comorbid conditions, such as ADHD, disruptive behavior disorders, and anxiety disorders.[86] Treatment of these disorders raises additional concerns, particularly when a comorbid condition also requires intervention with psychotropic medications. Most often, clinicians recommended that bipolar symptoms be stabilized before any additional medications are introduced to address comorbid conditions.[112, 125] Additional medications that were added once bipolar symptoms were stabilized, particularly psychostimulant medications used to treat ADHD, showed promising results.[130, 137] In particular, mixed amphetamine salts were significantly more effective than placebo for treating ADHD symptoms in 6 to 17 year olds with a bipolar I diagnosis.[139] Nonetheless, some medications (i.e., antidepressants) should be monitored closely. Although many suggested that antidepressant-induced bipolar symptoms may occur uncommonly (e.g., see 140, 141), some children and adolescents may be susceptible to such symptoms.[142]

As previously mentioned, although the use of psychotropic medications is increasing in the preschool population, these medications have not been studied adequately.[143, 144] In the limited research that was conducted with preschool children, several of the commonly used medications that were effective in older children also appeared to be effective in this population. Specifically, studies investigating risperidone, olanzapine, valproate, divalproex sodium, and carbamazepine all showed positive results.[70, 145–147] In contrast, lithium may not be as effective as these other medications.[126] Further studies suggested that psychostimulant medications used to treat comorbid ADHD symptoms prompt clinically significant changes in preschoolers' behavior and are well tolerated by individuals in this age group.[148] To verify such results, more research using randomized control trials is warranted.

Cognitive-Behavioral and Psychosocial Interventions:

Despite the recommendation that psychotherapeutic interventions be used as an adjunct to psychopharmacological interventions in order to address psychosocial factors that may accompany bipolar symptoms,[137] research investigating the use of psychotherapeutic interventions with childhood-onset bipolar disorder was sparse. Overall, the primary psychotherapeutic interventions for childhood-onset bipolar disorder focused on the role of high emotion expression in families (e.g., critical remarks, hostility, and overprotection). Specifically, these treatments posited that these behaviors had detrimental effects on children with bipolar disorder and may encourage negative reactions in children (e.g., temper tantrums, self-destructive behavior). These negative reactions, in turn, exacerbated further high emotion expression behaviors.[149, 150] **Thus, many of the psychotherapeutic interventions available sought to address dysfunctional communication styles within families that might exacerbate the presence of bipolar symptoms and to teach families about the management of bipolar disorder via psychoeducation[151] in either individual or group settings.[149]** Additional areas of focus for

psychotherapeutic intervention included relapse prevention, individual psychotherapy, social functioning, and academic functioning.[137]

Generally, research suggested that cognitive-behavioral interventions (i.e., those that address the aforementioned topics) are feasible and efficacious with children and adolescents with bipolar disorder.[152, 153] In fact, researchers are beginning to develop specific psychotherapeutic programs that utilize the cognitive-behavioral theoretical framework. One such example is the "*Think Effectively about Mood Swings* (TEAMS)" program.[154] This program is based on an integrative cognitive model that suggests that multiple and extreme appraisals of internal state changes and the impact that these changes have on behavior, physiology, and the environment actually maintain and exacerbate bipolar symptoms. By addressing the extreme positive and negative appraisals of internal state changes through cognitive-behavioral therapy, bipolar symptoms were improved.[154] Although this particular program was examined in a small sample of adults, such programs may have applicability for children (and preschool children) if adapted for their developmental levels.

An additional therapy that may prove useful for treating symptoms of bipolar disorder in children may be an adaptation of *Dialectical Behavior Therapy* (DBT), a treatment designed originally for Borderline Personality Disorder,[155] given its focus on mindfulness and distress tolerance skills. For example, Goldstein and colleagues[156] conducted a one-year open trial of DBT with adolescents who had bipolar disorder using both family skills training and individual therapy. Although their open trial included only ten adolescents, their study suggested that the feasibility and acceptability of using DBT were high and that the adolescents exhibited significant improvements in their symptomatology (e.g., suicidality, self-injurious behavior, emotional dysregulation, and depressive symptoms) in conjunction with the intervention.[156]

Finally, new therapies are beginning to focus on the difficulties that children and adolescents with bipolar disorder have with the rhythmicity of their behaviors (e.g., in sleep, behaviors, and mood episodes). One such therapy is *Interpersonal Social Rhythm Therapy* (IPSRT),[157, 158] a therapy that was derived from interpersonal psychotherapy for depression and behavioral intervention for social rhythm and sleep-wake regulation. The underlying premise of this therapy is that individuals with bipolar disorder need to recognize the relationship between disruptions in social rhythms and the onset of previous mood episodes. They then can use behavioral interventions to make improvements in their social rhythms and sleep-wake regularity.[158] Research suggested, thus far, that IPSRT is a useful adjunct to pharmacological interventions, that it can extend the time between mood episodes, and that it can improve individuals' social rhythms.[158]

Family Interventions

In addition to addressing these treatment areas, family interventions also can be helpful, particularly for families who are raising children with bipolar disorder. For example, *Multifamily Psychoeducation Groups* (MFPG) and *Individual Family Psychoeducation* (IFP) were provided as a potentially useful treatment for childhood-onset bipolar disorder. MFPG and IFP included education about bipolar symptoms and symptom management, the improvement of communication skills among family members, and the increase of support among family members.[151] MFPG was designed for implementation in group settings. Such settings provide the opportunity for children to augment their social skills and for parents to gain support from other families. Each session began with all of the families together before children and parents participated in their own groups. The child and parent groups then covered similar topics but addressed the specific needs of each group.[149] For parents, topics included education regarding their children's bipolar symptoms, medications, community services, family communication, problem solving, coping skills, and symptom management. For children, similar information was provided but focused more heavily on improving children's skills through applied practice.[159]

IFP was developed so that the needs of families could be addressed on an individual basis. This treatment protocol utilized alternating child and parent sessions (rather than completing both sessions concurrently). The content of treatment sessions was similar to that provided in MFPG. In contrast, families also were

provided with additional information regarding healthy habits (e.g., sleep hygiene, nutrition, and exercise). In addition, although this treatment was manualized, several sessions were built into the treatment protocol so that topics could be personalized for individual families.[159] Both the group and individual formats of this treatment effectively demonstrated symptom decreases in children who ranged in age from 8 to 11 years.[151,160] Given these findings, this treatment protocol should be examined further for families who have children with bipolar disorder.

An additional family treatment, the *Family Focused Treatment* (FFT) protocol, was adapted for use in adolescents from a treatment that already had proven successful in adult patients. The goals for this treatment protocol focused on increasing the understanding of mood symptoms, improving medication compliance, enhancing communication skills, and reducing social impairment. Treatment sessions were divided into three modules that included psychoeducation, communication skills, and problem-solving skills. During the psychoeducation module, families were provided with information regarding symptoms, mood tracking, and risk factors. Families also developed a tailored intervention plan to prepare them for instances of symptom relapse. During the communication and problem-solving skills modules, families were provided with strategies to decrease negative communication styles and to increase cooperative family problem solving. Research indicated that this treatment demonstrated significant symptom reduction in adolescents.[150] Thus, with adaptations for families with children, this treatment protocol may have some utility.

As a final family intervention example, the *Child and Family Focused Cognitive-Behavioral Therapy* (CFF-CBT) protocol was developed as a downward extension of FFT for children (i.e., those who ranged in age from 8 to 12 years) and their families.[133] The treatment protocol incorporated cognitive-behavioral techniques (e.g., problem solving, positive self-view), interpersonal techniques, and psychoeducation. Sessions were structured around children only, parents only, and combined child and parent activities. This treatment protocol also emphasized the inclusion of siblings by providing them with information regarding childhood-onset bipolar disorder in an effort to increase their empathy for their affected siblings. Finally, the therapist worked with the children's school to provide education and appropriate school-based interventions. Efficacy research demonstrated symptom reduction when this treatment protocol was provided both individually,[133] and in groups.[153] Additionally, this treatment was somewhat effective with children who were as young as 6 and 7 years of age.[153] These gains were sustained when a maintenance phase was added to the treatment. This maintenance phase included psychotherapeutic booster sessions and assistance with medication management.[161] Such family interventions may hold particular promise for use with families who have children with bipolar disorder given the strong evidence base of these interventions.

Treatment Summary

Although no interventions were validated for use with children, particularly preschool children, who have bipolar disorder, many of the techniques that were used in the aforementioned intervention programs could be useful, particularly if they were modified to be more developmentally appropriate (e.g., accounting for potential cognitive limitations, emphasizing more behavioral components). Specifically, it would be necessary for any proposed treatment to emphasize the involvement of the entire family, particularly their caregivers. Because children rely so heavily on these individuals, it would be imperative for caregivers to understand the nature of bipolar disorder and the necessary actions for effective intervention.[162] Additionally, given the difficulties that are inherent in caring for children with bipolar disorder, it would be likely that caregivers would need a great deal of emotional support. Although children may not be able to participate in all of the cognitive-behavioral aspects of current treatments due to the potential for developmentally limited cognitive abilities, children still could benefit from instruction in emotion regulation strategies, distress tolerance skills, and developmentally appropriate information about their bipolar disorder. Further, because research suggested that children, particularly preschool children, can suffer from significant impairments in communication, daily living, and social

skills,[33] additional training via behavioral interventions in these areas would likely be very beneficial.

Conclusions

Although *DSM* criteria for bipolar disorder may have limitations in the context of diagnosing bipolar disorder in children, it is clear that children are receiving this diagnosis. Nonetheless, to improve the developmental appropriateness of the diagnostic criteria that are currently available for bipolar disorder when used in children, particularly preschool children, other considerations should be made. Clearly, the subtypes described by Leibenluft and colleagues[46] and the idea of a bipolar disorder spectrum may be helpful in more carefully defining bipolar disorder in children; however, the prevalence of certain symptoms at young ages and the degree of emotion dysregulation that children, particularly preschool children, may exhibit also should be considered. As adjustments are made in the diagnostic criteria used to label bipolar disorder in children, further recommendations to the assessment process can be added to those already provided by the Practice Parameter[108] and by Baroni and colleagues.[109] Most importantly, however, more progress needs to be made in developing and identifying those interventions, whether via pharmacological interventions and/or family-based cognitive-behavioral interventions, that will treat the symptoms exhibited by children with bipolar disorder most efficaciously. It is only through clearly defining, identifying, and consequently remediating these bipolar symptoms that children can benefit from a more positive trajectory as they proceed through their developmental milestones into later childhood, adolescence, and ultimately adulthood.

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

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Multiple-Choice Questions

17. According to the lesson, a more useful and expedient tool recommended to detect bipolar symptoms in children via rating scales provided by parents is the:

A. *Kiddie Schedule of Affective Disorders and Schizophrenia* (KSADS)

B. *Child Mania Rating Scales*

C. *Diagnostic Schedule for Children* (DISC)

D. *Parent General Behavior Inventory* (GBI)

18. Which one of the following medications is approved by the FDA to treat mania in children who are 12 years and older?

A. Risperidone

B. Aripiprazole

C. Lithium

D. Olanzapine

19. According to the lesson, when managing children with bipolar disorder who also present with symptoms of another comorbid disorder such as ADHD, most clinicians:

A. focus on treating the comorbid disorder.

B. attempt to stabilize the bipolar symptoms before introducing other medications to address the comorbid conditions.

C. treat symptoms of both disorders using low doses.

D. administer CBT interventions prior to any medication.

20. Many psychosocial interventions for childhood-onset bipolar disorder focus to address:

A. dysfunctional communication styles.

B. psychoeducation of bipolar disorder among families.

C. relapse prevention.

D. All of the above

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Best Practices in CME

Bipolar Disorder in Children, Part 2: Assessment and Interventions

By Kimberly Renk, PhD; Rachel White; Brea-Anne Lauer; Meagan McSwiggan; Jayme Puff; and Amanda Lowell

ID#: L903347

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

CME Lesson Overview

This lesson aims to assist health glean a snapshot of the literature in this area so that they can gain an understanding of the diagnostic criteria and other behaviors that may be relevant and be informed about potential approaches for assessment and treatment with children who meet bipolar disorder criteria.

Key Point 1: Background

Although bipolar disorder historically was thought to only occur rarely in children and adolescents, there has been a significant increase in children and adolescents who are receiving this diagnosis.

Key Point 2: Assessment Tools

Specific assessment tools such as the *Kiddie Schedule of Affective Disorders and Schizophrenia* (KSADS), the *Diagnostic Interview Schedule for Children* (DISC), and the *Child Mania Rating Scales* can be used to assess bipolar disorder. Further, studies suggest that specific parent rating scales, such as the *Parent General Behavior Inventory* (GBI), the *Young Mania Rating Scale* (YMRS), and the *Child Behavior Questionnaire* (CBQ) be used instead of structured interviews which may take a significant amount of time and expense to administer.

Key Point 3: Psychosocial Intervention

Psychosocial interventions are often used as adjuncts to pharmacological treatment. Such interventions aim to address dysfunctional communication styles that may exacerbate the presence of symptoms, psychoeducation of bipolar disorder among family members to increase understanding and enhance medication compliance, and relapse prevention, among others goals.

Key Point 4: Pharmacological Treatment

The most commonly prescribed medications for children and adolescents who exhibit bipolar symptoms were lithium, antiepileptic medications i.e., divalproex sodium and carbamazepine), and atypical antipsychotic medications (i.e., risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole). Of these medications, lithium is approved by the FDA to treat mania in children who are 12 years of age and older, whereas risperidone and aripiprazole are approved for children who are 10 years of age and older.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Behavioral Activation for Depression

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No commercial support was used in the development of this continuing medical education lesson.

KEY WORDS: Depression • Activity Monitoring • Activity Scheduling • Avoidance

LEARNING OBJECTIVES: Upon completion of this lesson, readers will be able to: (1) define and describe behavioral activation, (2) implement activity scheduling with depressed patients, and (3) employ techniques to counter avoidance in depressed patients.

ABSTRACT: When treated with pharmacotherapy, many patients with depression have significant residual symptoms that impair their lives and increase the odds of depressive relapse. Behavioral activation is an approach to treating a depressed patient that may be used in conjunction with many types of interventions. It is a practical and empirically supported treatment. Key elements of behavioral activation include activity monitoring, activity scheduling, and particular techniques that address rumination and avoidance behaviors that are frequently associated with depressive illness. These techniques are employed in the context of a collaborative therapeutic relationship that acknowledges the lack of motivation so common in depression while employing behavioral strategies to overcome inertia.

COMPETENCY STATEMENT: This lesson addresses a gap in learning in the area of knowledge, patient care, and practice-based learning and improvement. Many clinicians struggle to help patients attain full recovery from major depression. Residual symptoms are common and disabling, and they incur a higher risk of relapse. Behavioral activation is an underused tool that can treat depression as a standalone modality or enhance patient response to pharmacotherapy.

Introduction

The term "behavioral activation" was coined by Hollon and Garber in the 1990 paper, "Cognitive Therapy for Depression: A Social Cognitive Perspective," in which they emphasized that therapists should focus on behaviors and actions to test the underlying beliefs of a depressed person.[1] Although the phrase is relatively new in psychotherapeutic literature, the principles of behavioral activations have been used for decades. Behavioral activation is a set of clinical procedures that facilitate engagement with pleasurable, meaningful and important activities, that when used in depression treatment have a profound effect on symptoms.

Treatment Development and Empirical Support

The underlying principles and scientific foundations of behavioral activation took shape in the last four decades.

Early Studies:

In 1973, Ferster proposed that avoidance, escape, and the absence of positively reinforced behavior were the basis of depression.[2] His work was derived from the behavioral principles of B.F. Skinner's seminal work, which linked depression with the disruption of healthy behavior.[3] **Lewinsohn, who started his work on behavioral activation around 1965, tried to provide empirical evidence for this new theory. In his 1973 paper with Graf, he postulated that a depressed person experienced an increase in aversive events and a decrease in pleasant events.[4] In 1984, he proposed that a decrease in the frequency of positive reinforcement and an increase in the frequency of punishment were the basis of depression.[5] This work further emphasized the importance of cognitive restructuring in helping a patient engage in fundamental behavioral activation strategies along with skill training including social skills, problem solving, and assertiveness.** Beck et al., in the 1979 groundbreaking work, *Cognitive Therapy of Depression*, included treatment of behavioral dysfunction as a core principle of the treatment of depression.[6]

Empirical Research and Contemporary Practice:

By 1990, a significant overlap in behavioral and cognitive theories of depression had occurred. By the mid-1990s, Jacobson et al.[7] empirically evaluated the components of *cognitive behavioral therapy* (CBT) for the treatment of depression. This randomized controlled trial determined that cognitive changes may occur following behavioral activation alone and established behavioral activation as a standalone treatment for depression. Jacobson et al. showed that behavioral activation was equal to cognitive therapy for both treating depression and modifying negative thoughts and maladaptive behaviors. A two-year follow-up study found no significant differences between different treatment arms in terms of relapse rate, time to relapse, or the number of "well weeks,"[8] clearly establishing behavioral activation as a durable and effective treatment for depression. Subsequently, two independent studies by Hollon and Otto[9,10,11] showed that the most significant improvement in depression symptoms in standard CBT happened during the initial phase of treatment, during which behavioral techniques are most commonly used. This cemented the role of behavioral therapy as a robust standalone treatment for depression.

Following these early studies, there has been an exponential increase in the number of research papers about behavioral activation. Dimidjian et al. (2006) showed that the treatment of severely depressed patients with behavioral activation was comparable to antidepressant medication treatment alone and was more efficacious than cognitive therapy alone.[12,13] A two-year follow-up study in 2008 showed no statistically significant differences between the durability of response in behavioral activation and cognitive therapy, and both therapies were superior to medication in preventing a relapse of the symptoms of depression.[14] Hopko et al.[15] and Curran et al.[16] found evidence for the efficacy of brief behavioral activation treatment for depression in an inpatient setting. Behavioral activation is a well-established, empirically validated treatment for depression. It works as a powerful, efficient tool to increase a patient's ability to participate in enjoyable and meaningful activities, which results in an improved mood and a return to normal functioning.

Dissemination of Behavioral Activation:

In 2009, the *National Institute for Health and Clinical Excellence* (NICE) included behavioral activation as a treatment for depression in its evidence-based treatment guidance section.[17] Addis and Martell (2004) published a self-help book, *Overcoming Depression One Step at a*

Time, based on the principles of behavioral activiation.[18] Other authors have adapted behavioral activation for the treatment of other conditions. Mulick and Naugle used behavioral activation in 2004[19] to effectively treat post-traumatic stress disorder. Daughters et al. and MacPherson et al. used behavioral activation techniques in 2008[20] and 2010,[21] respectively, to treat depression arising from comorbid substance abuse.

Clinical Application of Behavioral Activation

Key Elements in Implementing Behavioral Activation:

Don't Leave Your Therapy Skills Behind!

All cognitive and behavioral interventions, including behavioral activation, are meant to be delivered in an individualized and tailored manner and in the context of an empathic therapeutic relationship. This ensures that patients are more likely to adhere to therapeutic recommendations. One of the most important aspects of working with depressed patients is conveying to them a real sense that you understand how difficult everyday tasks have been and how little pleasure they feel in life but that you are confident that working to accomplish these activities in a systematic way will help them to recover.

Explain the Rationale for Behavioral Activation

Explaining why a particular procedure is recommended and what it is designed to achieve is a cornerstone of effective CBT and part of the approach in behavioral activation. Patients who understand the reason for interventions are more likely to participate in them. Patients will also use interventions during times of distress in the future if they learn the principles behind the activity, thus protecting against relapse. One goal of behavioral activation in particular (and CBT in general) is that a patient should learn the tools of therapy so they can use them for a lifetime.

The first part of how to explain the rationale for behavioral activation to patients is as follows:

> Most people who are depressed are aware of the natural tendency to want to do less, isolate, and withdraw when feeling sad. Emotions serve to get our attention and orient us to take action. However, taking action that follows emotional cues is not always in our best interests. If I am angry at someone and punch them in the nose, it may not be the most useful course of action! Following the tendency to withdraw when I am depressed will ultimately produce even more depression both because of the lack of positive interactions that will result and because of significant life consequences I will incur (for example, getting fired).

The depressed person who does less naturally concludes that he/she is helpless. So, although initially avoiding life pursuits may feel good and like a relief, it is eventually much worse. Additionally, clinicians can tell patients that research has shown that engaging in pleasurable and meaningful activities helps to treat depression.

Part two of explaining the rationale is to say that many believe that action follows a feeling of "having motivation." When a task is perceived as difficult, we often delay action until we "feel" like doing it. This is a fallacy. Actions do not need to follow feelings. Most of us have had many activities we accomplished despite not feeling "motivated." By discussing these principles with the patient and obtaining examples (for example, waking up in the middle of the night to care for a child, going to work on a Monday morning, or attending a weekend work seminar), the patient can engage with the idea that action can occur following a plan, not a feeling.

Finally, the therapist must join with the patient and express that although contemplating any action may seem difficult in the current mood state, the therapist is an expert in helping people change behavior. The plan is for the therapist and patient to work together to help the patient begin to do important and pleasurable things.

Find Out What the Patient Is and Is Not Doing and What Was Rewarding Prior to Being Depressed

In addition to interviewing the patient, patients should be instructed to monitor their activities for a day or two (a weekday and weekend day if normally scheduled activities on those days are different—for example, if the patient is working) to provide data regarding what to plan to activate. Such detailed monitoring should occur hourly and contemporaneously. The rationale for hourly monitoring is that depressed patients have faulty memories; recall can be skewed by mood, and significant events may be omitted if the patient waits to fill out

the log until the end of the day. Smartphone apps or paper logs may be used to record activity. It is essential to explain the rationale for this level of detail to the patient to gain cooperation. Here is a good example of such an explanation:

> One thing we really need is a good example of what an average day is like for you. In order to do this, I'm going to ask you to jot a few words down every hour about how you spend your time. I'd like you to do it every hour because it would be easy to forget important things you do by and at the end of the day. Things that were associated with a good mood or a low mood could also be neglected if you don't do it hourly depending on your mood at the end of the day. I don't need you to do any elaborate writing—just a word or two. Do you think that would be possible?

Activity monitoring may also occur in a more informal way even in briefer sessions—a good metaphor to use with patients who had prior stable mood and good functioning is to ask, *"If we had a time machine and traveled back to a time in your life when you were doing well, what would you be doing on a typical day?"*

Activity monitoring may also determine whether the patient derives enjoyment or a sense of accomplishment from activities if modified specifically for this purpose. This intervention may help patients "tune in" to pleasure and recognize accomplishments. Ask patients to develop a scale with you and rate from 0-10 (using the anchor points of 0 being neutral and 10 being the maximum pleasure or sense of accomplishment) the degree of enjoyment or sense of accomplishment they feel with any activity. This helps patients to target either anhedonia or a sense of futility. Patients should rate the sense of accomplishment or the amount of enjoyment they perceive in their *current* state of mind, not when they're in a normal mood state, so any mastery or any sense of pleasure is a forward step. Remember, patients who are depressed don't experience pleasure for a number of different reasons. First, they engage in fewer pleasurable activities. Second, they do not notice pleasurable sensations (which this procedure targets). Finally, they have interfering cognitions that interfere with pleasure—for example, they may have thoughts such as *"I don't deserve to feel pleasure"* or *"I shouldn't have pleasure because I will feel depressed later."* Depressed patients also devalue accomplishments and have thoughts like, *"I should not receive credit for this small amount of activity,"* even though that activity might be extremely difficult to accomplish when they are depressed.

Use mastery and pleasure ratings only after the patient has successfully recorded one day of activities. Once data is obtained about patient activities, you can proceed to the next critical step: case conceptualization and activity scheduling.

Develop an Individualized Case Conceptualization

Once clinicians have a sense of the patient's behavioral excesses and deficits—i.e. what the patient is and is not doing; what they have stopped doing; how the patient's current activities affect his mood; and whether there are any specific avoidance patterns, deficits, or skills problems (e.g., social skills deficits)—the next step is to construct a hierarchy of activities from least difficult to most difficult. This list should contain a variety of tasks—for example, those that the patient values, those that are pleasurable, activities of daily living, or core life activities like going to work. Be mindful of the presence or absence of routines—one thing of significant importance in patients with chronic depression is whether there is a lack of routine. This may lead to significant problems; patients experience a struggle with daily decision-making and confusion regarding how to spend time most beneficially in accomplishing everyday tasks. Establishing routines about things like grooming, shopping, household tasks, and self-care is extremely helpful to chronically depressed patients and frees them to do many more pleasurable and important activities.

Sometimes, patients are unable to identify positive and pleasurable activities to pursue when they are depressed. One can use lists of potential pleasant events (i.e., a pleasant events schedule) to help the patient identify pursuits that they have previously enjoyed that may be activated. Additionally, some patients who are depressed may say that they are engaging in a number of activities that are normally seen as pleasurable (like watching television) in order to avoid more demanding activities. This needs to be corrected as well. Often, thoughts that activities are "too difficult to tackle" derail patients from action. This inaction perpetuates a sense of futility and lack of accomplishment.

Use the Activity Hierarchy to Assign Tasks

Scheduling activity is the core component of behavioral activation. From the activity hierarchy, you and the patient collaboratively agree to attempt several items in the next week. The number of items assigned per session depends on session length and the degree of mood disturbance. The rationale is reiterated; reconnecting with important and pleasurable life tasks is key to recovering from depression. Skills required for the clinician include monitoring that the assignments have just enough challenge given the patient's level of current function. The patient must not be overwhelmed, so breaking the activity into parts and doing one small part at a time are often necessary. In addition, thoughts that an activity is too easy will increase a patient's distress and self-criticism. In such circumstances it is necessary to explain that small amounts of effort while recovering from such a significant illness are to be applauded. Assignments should be manageable so that task implementation is likely to be successful. Think of Goldilocks—ask patients if the task is too overwhelming, too easy, or just right.

Troubleshooting Action Prescriptions

One common myth about behavioral activation is that it is a version of saying "*just do it*" to patients. It is not so simple. Clinicians are experts in behavior change and therefore have a variety of proven methods to help patients succeed. Strategies that are helpful to engage patients in practicing activities include:

- **Collaboration and encouragement (*"let's think of one or two things to try this week that might improve your mood"*; *"remember that the goal is doing what's important to you"*).**
- **Stimulus control is of great importance in adhering to the plan—make assignments concrete, specific, and in writing.**
- **Troubleshoot any potential obstacles to completion in the session—really give the patient time to think about what might get in the way of engaging in the activity. Ask the patient what he/she would do if something happened to derail the plans—for example, if the plan is to take a walk, ask, *"What will you do if it is raining?"***
- **Cognitive rehearsal/imagery regarding the activity assignment: This technique walks the patient in his/her mind through the steps leading to completing the task and checks the ability of the patient to plan and execute the task. It can identify roadblocks and negative predictions so that it is more likely that the assignment will be completed.**
- **Public commitment to doing any task increases adherence; get the patient to agree that the activity will happen.**
- **Increase accountability and focus therapy time on the previous assignments.**
- **Contingency management includes planning rewards or having friends or family participate in the activity. Rewards are particularly useful when the activity is not very rewarding in itself.**

Validation

Validation deserves a special mention as a strategy to engage the patient. If the obstacle the patient raises is that he/she "doesn't feel like doing things" (a common difficulty with depressed patients), reiterate the rationale that this response is natural in depression. Then, emphasize that one way out of depression is to act from the "outside in"—that is according to a plan. Another useful strategy is to ask the patient to recall times when he did something even when not "motivated." Everyone has instances of accomplishing things we didn't "feel like doing." Stress the consequences of continuing inactivity.

Make Certain Increased Activity Is Routine Before You Move Forward:

Activity scheduling is often abandoned too soon in a course of therapy for depression. Subsequent sessions should include assigning three to five assignments per session, discussing one or two in detail. Types of reminders of the agreed-upon activities vary from patient to patient—they can be visual or auditory (cell phones or calendars) and should include as much detail as possible. Once activity scheduling takes hold, move up the hierarchy to do things that are either more difficult or

more frequently avoided. Avoidance often has significant negative life consequences—choosing and planning alternatives and observing how life improves can break this cycle.

Behavioral Activation in "the Real World"

The following case example illustrates the principles of behavioral activation in practice.

> **A 22-year-old man presented for treatment of depression. He stated that his symptoms started a few years ago after he was rejected during tryouts for a semi-professional basketball team. It had been his lifelong dream to play basketball as a career after high school. He was the star center for his high school team, which won several championships. He was recruited to play for a prestigious college team on a full scholarship, but he was only able to play for one year as he was dismissed from college for poor academic performance. He subsequently withdrew socially and stated that he was "totally demoralized." He did try out for a few semi-professional teams after this, but he stated that he was not selected, and he felt his performance declined because he stopped practicing following his college dismissal. He then obtained a job as a salesman at a clothing store but was fired for poor performance and frequent absences. He had been unemployed for a year and a half at the time he presented for therapy.**

At the time of first assessment, the patient was spending most of his time staying at home watching TV and playing video games. He stated that he had many friends in high school and college and was always going to parties and "hanging out" on weekends, but currently he had little interest in seeing his friends. In addition to depressed mood and anhedonia, he had crying spells and insomnia. He stated that he was most depressed when he was alone because he ruminated about his lost basketball career and what his life could have been had he been able to play professionally.

During the initial session, the concept of behavioral activation was introduced as well as psychoeducation about depression. He was briefed about how his depressed mood caused him to want to do less and how this manifested itself in his social withdrawal and his avoidance of positive activities in favor of avoidance behaviors such as watching TV and playing video games all day. He was able to observe that when he watched TV, it actually did not provide any relief of his low mood. The psychiatrist pointed out that by withdrawing socially, the patient was making his depression worse. Behavioral activation was introduced as a way to break this cycle and help improve his mood. It was explained to him that to increase activation and recover from depression, the impetus for behavior should be goal directed rather than mood directed—an "outside-in" approach for behavior change. He was asked to complete a baseline activity log for two days to assess how he spends his time and its relationship to his mood.

During the second session, the rationale of using an activity schedule was reiterated. On examining his activity log, his social avoidance was clear—he refused chances to socialize with his old friends and was not answering phone calls or text messages. His sleep cycle was derailed by his staying up much of the night and sleeping until mid-afternoon. He engaged in near-constant rumination about his lost basketball career. A hierarchy of activities, including pleasurable activity, self-care and important life activities, was constructed from least difficult to most difficult. These activities addressed his specific avoidance patterns that contributed to his depression.

The patient started to work collaboratively on the plan with an initial emphasis on self-care: doing laundry, and shopping. The tasks were broken down into very small

Table 1:
Activity Hierarchy

Activity	Anticipated difficulty (1-10)
Going to movie with a friend	9
Eating out with a friend	9
Calling any of the old friends	7
Talking to someone in the street	6
Buying new clothes from the mall	6
Shopping from local grocery store	5
Exercising at home with weights	4
Doing laundry	3
Brushing teeth, showering, and changing clothes	2

steps, and obstacles were identified. Certain reminders were introduced like setting an alarm in the morning to start his day and placing postings on his refrigerator for the plan to do laundry. He was also introduced to the principle of mastery and pleasure ratings, and troubleshooting was done in the sessions to overcome obstacles. Since the main triggers for his rumination about the past were being alone in his room and watching baseball on TV, he was instructed to engage in activities that were fairly engrossing (vigorous exercise with weights) when he noticed he was ruminating. Also, the rumination of "if only things had been different and my basketball career had worked out" was turned into the question of "how to have a fulfilling life even though his basketball career would never be what he had hoped." His values and goals were also examined to see other sources of fulfillment in his life. He identified working with children as highly important to him. He decided that his long-term goal was to become a high school basketball coach and his short-term goal was to volunteer at Little League at least one day a week.

Following successful completion of the first five assignments, he felt ready to target his social avoidance. He was assigned the task to call at least one friend a week with a goal of planning at least one activity with a friend outside of the house per week. The planned activities were going to eat at a nearby fast-food chain, which he previously loved to do, and going to a movie. Cognitive rehearsal was employed to identify obstacles. He listed a number of things that he thought could go wrong, troubleshooting these in the session in order to prepare him for his task. He was coached to practice skills to execute his plan and, if needed, to make necessary accommodations. He called a friend and asked him to go out to lunch. Unfortunately, his friend could not join him because he had to work. Because he and the psychiatrist did troubleshooting about the plan, he was ready with an alternative plan and asked his friend to meet with him the following week to watch a basketball game on TV. The patient became anxious prior to watching the game with his friend and was about to cancel, but he went through with the plan, reminding himself of the idea that he did not need to be motivated to do so. He watched the game with his friend and enjoyed it. During the evening, he was told that another mutual friend had a fracture due to an accident and was unable to leave his house. He decided to visit him the next day and enjoyed spending time with him.

In the session following this, he said he felt much better that he was able to socialize with his old friends. He was troubled by his inability to enjoy things outside of his planned activities. It was explained that it may take some time and perseverance until his mood lifts.

Summary

Behavioral activation is a well-established, empirically validated treatment for depression. It works as a powerful, efficient tool to increase a patient's ability to participate in enjoyable and meaningful activities, which results in an improved mood and a return to normal functioning.

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Multiple-Choice Questions

21. In a randomized clinical trial of behavioral activation for acute treatment of adults with major depression in 2006, Dimidjian et al. found which of the following among more severely depressed patients?

A. Behavioral activation was ineffective.

B. Behavioral activation was less effective than medication.

C. Behavioral activation was less effective than cognitive therapy.

D. Behavioral activation was comparable to antidepressant medication.

22. In 2008, a randomized clinical trial for prevention of relapse and recurrence in major depression found which of the following?

A. There were no statistically significant differences between the durability of response in behavioral activation and cognitive therapy.

B. Psychotherapies are more expensive than antidepressants.

C. Psychotherapy is less durable than medication in the treatment of depression.

D. Psychotherapy is less desirable to patients than antidepressant medication.

23. What strategy do clinicians use when asking patients to imagine the steps involved and obstacles possible in executing a given task?

A. Task planning

B. Cognitive rehearsal

C. Imagery rescripting

D. Guided discovery

24. Strategies to engage patients to effectively complete activity assignments, particularly when activities are not very rewarding in themselves, include:

A. contingency management.

B. token economies.

C. thought records.

D. negative reinforcement.

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Best Practices in CME

Behavioral Activation for Depression

By Donna M. Sudak, MD; M. Hassan Majeed, MD; and M. Khalid Zafar, MD

ID#: L003349

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

CME Lesson Overview

Behavioral activation is a well-established, empirically validated treatment for depression. It works as a powerful, efficient tool to increase a patient's ability to participate in enjoyable and meaningful activities, which results in an improved mood and a return to normal functioning.

Step 1: Explain the Rationale

Most depressed patients are aware of the natural tendency to want to do less, isolate, and withdraw when feeling sad. However, taking action that follows emotional cues is not always in our best interests. The consequence is that our life gets worse and we feel more depressed when we do less.

Step 2: Monitor Activity

Patients should monitor their activities for a day or two (a weekday and weekend day if activities are typically different between weekend and weekdays) to provide data regarding what to plan to activate. Such detailed monitoring should occur hourly and contemporaneously.

Step 3: Make an Activity Hierarchy

Construct a hierarchy of activities from least difficult to most difficult. This list should contain a variety of tasks— for example, those that the patient values, those that are pleasurable, activities of daily living, or core life activities like going to work.

Step 4: Assign Activities

Scheduling activity is the core component of behavioral activation. From the activity hierarchy, collaboratively agree to attempt several items in the next week. The number of items assigned per session depends on session length and the degree of mood disturbance. The assignment should be written and detailed in the session, and obstacles should also be discussed and solved in the session. The rationale is reiterated; reconnecting with important and pleasurable life tasks is key to recovering from depression.

Step 5: Troubleshoot Assignments

Give the patient time to think about what might get in the way of engaging in the activity. Ask the patient what they would do if something happened to derail the plans—for example, if the plan is to take a walk, ask, "What will you do if it is raining?"

Step 6: Make Certain Activity is Routine

Once activity scheduling takes hold, move up the hierarchy to do things that are either more difficult or more frequently avoided. Avoidance often has significant negative life consequences—choosing and planning alternatives and observing how life improves can break this cycle.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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The Changing Landscape of Care: Does Ethics Education Have a New Role to Play in Health Practice?

Julie Wintrup

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

KEY WORDS: Healthcare education • Ethics education • Professional ethics • Moral agency • Ethical self-formation

LEARNING OBJECTIVES: Upon reading this lesson, clinicians will (1) examine the way ethics education is designed in a changing healthcare environment, and (2) consider how ethics education that promotes moral agency, rather than problem solving approaches, would explore not only clinical problems, but also the difficult and contested arenas in which they occur.

LESSON ABSTRACT:

Background: In the UK, higher education and health care providers share responsibility for educating the workforce. The challenges facing health practice also face health education and as educators we are implicated, by the way we design curricula and through students' experiences and their stories.

This paper asks whether ethics education has a new role to play, in a context of major organizational change, a global and national austerity agenda and the ramifications of disturbing reports of failures in care. It asks: how would it be different if equal amounts of attention were given to the conditions in which health decisions are made, if the ethics of organizational and policy decisions were examined, and if guiding collaborations with patients and others who use services informed ethics education and its processes?

Discussion: This is in three parts. In part one an example from an inspection report is used to question the ways in which clinical events are decontextualized and constructed for different purposes. Ramifications of a decision are reflected upon and a case made for different kinds of allegiances to be developed. In part two I go on to broaden the scope of ethics education and make a case for beginning with the messy realities of practice rather than with overarching moral theories. The importance of power in ethical practice is introduced, and in part three the need for greater political and personal awareness is proposed as a condition of moral agency.

Summary: This paper proposes that ethics education has a new contribution to make, in supporting and promoting ethical practice—as it is defined in and by the everyday actions and decisions of practitioners and people who need health services. Ethics education that promotes moral agency, rather than problem solving approaches, would explore not only clinical problems, but also the difficult and contested arenas in which they occur. It would seek multiple perspectives and would begin with places and people, and their priorities. It would support students to locate their practice in imperfect global contexts, and to understand how individual and collective forms of power can influence healthcare quality.

COMPETENCY AREAS: This lesson discusses the role of ethics education in a changing healthcare environment. The author considers the traditional approach of ethics education and how educators can better convey the complexities of clinical practice in a changing environment.

Background

This lesson explores how ethics education in professional health programs contributes to safe, effective and ethical practice. It suggests ways in which educators might more directly support and promote the ethical self-formation of students across disciplines.

A greater focus on new professional responsibilities and self-awareness is argued for, given the changing organization of health and social care services in the UK as many more providers join what has been described as a 'marketplace'. The impact of economic decisions also requires a response by health professionals, who have a role in minimizing their effect on patients and on the quality of care and treatment. Finally the undermining effect of high profile inquiries into the neglect and mistreatment of vulnerable people by healthcare professionals is considered in light of the need to rebuild trust and confidence.

There is much work to be done. The attention on health services and the way we educate the workforce following the Francis report offers an opportunity to reflect on the meaning of ethical practice, and how it needs to promote more effectively the goal of high quality healthcare.

In part one I discuss how problematic constructions of interdisciplinary and patient/carer relationships influence healthcare and serve to create or perpetuate disciplinary divisions. The case is made for a more nuanced appreciation of the way cultural and organizational influences prevent more unifying forms of problem analysis, and I go on to make a case for more and different allegiances. In part two the attention being paid to the personal characteristics of healthcare workers is problematized in light of critiques of the 'values' agenda. A more politically informed analysis is proposed. Part three introduces the need for an enhanced and confident sense of moral agency, and considers ways in which the idea of ethical self-formation has a contribution to make. Connections are made between the intimate and immediate work of healthcare, and general trends that influence the way we view ourselves as professionals. New contributions by students to global communities of practice that offer inspiring and energizing visions of practice are seen as supporting a reflexive stance.

Finally the argument is outlined in brief for broadening and complicating the work to be done within professional ethics education, if it is to offer a critique of healthcare's more fundamental problems.

A necessarily brief and speculative introduction to such ideas is offered here in keeping with the scope of a journal paper. Its purpose is to generate reflection, discussion and collaboration among those interested in the education and practices of the health workforce, and in quality healthcare.

Discussion

New Allegiances:

In 2011 a press release by the *Care Quality Commission* (CQC) reported that a doctor in a National Health Service hospital prescribed water to patients who were at risk of dehydrating.[1] The report stated that other staff agreed to the practice because it 'worked' and that the ward was short staffed. A subsequent newspaper commented "nurses sometimes left patients so thirsty that the only way for doctors to ensure they had enough liquid was to add 'drinking water' to medication charts."[2]

I would like to reflect briefly on this as a way of thinking about some of the moral complexities of a particular situation, and how interdisciplinary relationships are viewed. Firstly, the doctor in question clearly wished to improve patients' health. Viewed as a doctor-patient interaction, and through more traditional ethical perspectives, the doctor's actions were caring and—in many ways—constituted an effective or pragmatic response to a difficult situation; by treating drinking water as medication, patients no longer risked dehydration. However the need to 'prescribe' water indicated a much broader set of ethical concerns on the part of the doctor. Considering the relationships *between* nurses, doctors, and patients (rather than merely thinking about nurses, doctors, or patients as individuals) gives a stronger sense of the mutually connected dimensions of such a decision, and the ways in which both doctors and nurses—and inevitably many other health professionals—were implicated in sustaining these unsatisfactory conditions.

The newspapers appear happy to conclude that the nurses involved were fundamentally uncaring. However research has shown that short staffing within a particular

ward is more often a cause of 'care left undone.'[3] If such underlying causes were a feature of the doctor's decision, prescribing water perhaps unintentionally perpetuated and even legitimized wider organizational deficiencies. In terms of team working and collaborative patient care, the general acceptance that 'it worked' indicates a degree of passivity or compliance.

Of course, speculating on an actual event is problematic and risks misconstruing or denying the deeply situated nature of moral problems. But we already know a good deal about the importance of relationships, within and amongst disciplines and across the entire community of practice, in particular with patients themselves and those who care about them. The Bristol Royal Infirmary inquiry[4] highlighted how distant, task-oriented relationships between professionals, managers, patients and relatives negatively influenced care and treatment. Personal and professional distances noted between nurses, doctors and managers in particular reflect other inquiry reports over many years.[5] Sir Robert Francis was criticized for blaming primarily front line staff rather than senior managers, who, it has been claimed, were complicit in the maintenance of the inadequate treatment regimes at Mid Staffordshire.[6]

Poor standards of care also reflect ineffective safety and governance mechanisms. While the last resort of whistleblowing remains available to staff, such high-risk activity is known to be very personally costly.[7] Even diligent and caring staff must fear the ramifications of speaking out or reporting colleagues. Such fears may lead people to alleviate the worst effects of dysfunctional situations rather than to challenge them. This is within contexts in which a powerful need to belong has been reported in nurse education[8] and complex social games have been found to determine medical career chances.[9] Much has also been reported on the toxic effect of bullying cultures, their influence on individual behaviors, and the ways in which emotionally unsafe environments perpetuate fear and silence.[10]

Moral strain—highly associated with feelings of helplessness and work-related stress—is found to exist among practitioners working with inadequate resources who feel the need to compromise personal standards.[11] 'Human factors' research highlights just how dangerous tiredness, inattention and fear can be and how errors rise when a blame culture is evident.[12] Twigg[13] provides a stark reminder of the low status accorded to physical care work and its delegation to the least powerful and most precariously employed members of the workforce. Add to this the overwhelmingly female composition of the direct-care workforce and it is easy to see why Colley[14] surfaces the potential for exploitation of those socialized to take responsibility for caring work.

Professionals operate, to use Holland's[15 (p155)] words, 'in a distinctive ethical sphere [that] places distinctive normative requirements on [them]'. In other words, they are required to adhere to and promote a set of rules and standards regardless of the wider environment—even when the conditions of their work impede or prevent their being able to do so. The CQC account allows ethical problems beyond the individual professional-patient relationship to be explored, bringing interdisciplinary relationships and obligations, manifestations of power and compliance, fear, cultural influences and corporate responsibilities within the domain of ethical practice and therefore, I argue, of ethics education.

Interprofessional education has been part of undergraduate health programs for many years and offers an early opportunity to learn about what Emmerich calls ethico-political problems.[16] It is most likely to be when priorities differ that teams most need to work together, yet are at most risk of returning to a discipline-focused default position. Equally, the participation of patients and people using services or caring for others offers a powerful contribution to ethics education across the entire educational journey, including the lifelong *Continuing Professional Development* (CPD) of experienced practitioners. When allegiances across boundaries develop and become a new norm, negotiated objectives and more rigorous decision making strategies necessarily become an everyday feature of professional work.

Power is Real:

Francis called for a 'safer, committed and compassionate and caring service,'[17 (p1416)] urging staff to 'put patients before themselves' and to 'be honest and open with patients regardless of the consequences for themselves'. These invocations paved the way for the Chief Nursing Officer's so-called 6Cs—Compassion, Commitment, Caring, Courage, Competence and Communication.[18]

While this may provide a useful mnemonic, this conception of 'values' is out of step with other important work in the area. For instance, Sackett[19 (p1)] has looked beyond the values of the professionals, to 'the unique preferences, concerns and expectations each patient brings to the clinical encounter'. In a similar vein, Valenti et al.[20] offer a thoughtful analysis of how compulsorily detained patients' values differ from those of staff, offering better ways to understand and manage ethical conflicts. Frameworks for studying conflicting values, including organizational conflicts and vested interests, came out of the work of Fulford et al.[21]

Health services are deeply affected by political and 'macro-ethical'[22] issues such as financial and resourcing decisions, contractual arrangements, and workforce changes. Yet despite Kennedy's[4] assertion that government-driven 'top down' change presents a risk to safe care and treatment, these topics are unlikely to find their way into ethics courses in health professionals' education, or—because of how the scope of practice is defined—even thought to be relevant.

As educators, whether primarily in practice or academic roles, we have a responsibility to more thoroughly prepare healthcare students for the realities of professional practice in an increasingly mixed economy of care with its bureaucracy, visibility, increasing forms of delegation, marketization and complex regulatory and governance arrangements. Lines previously drawn around what is considered to be 'ethical practice' may need to be redrawn to include a more astute understanding of moral responsibility and delegation in such uncertain and rapidly changing contexts.

If educational messages are focused primarily on 'shared values' or 'individual personal qualities' we risk ignoring the far more complicated interplay between people, policy directives, political ambitions and health outcomes. These phenomena directly affect how people *act*, and set certain limits on possible courses of action. Students—and experienced practitioners learning through CPD—might usefully be supported to learn more about and to question these broader structures and contexts.

A recent study that involved professionals 'mapping' their knowledge of older people's admission routes into hospital, to learn how unnecessary admissions might be avoided,[23] offers a critique of discipline-focused approaches. Practitioners' deep knowledge of parts of the service contrasted with partial or impressionistic understandings of other parts. The likelihood of a multi-professional/multi-agency response—to work more effectively across boundaries or to recognize and challenge contradictions in policy enactment—is much reduced in such circumstances. However 'good' the quality of care in narrow or specialist areas, and however caring the individual practitioner, practice that requires 'boundary-crossing' risks falling short of being ethical in this broader sense. Knowledge and influence beyond single parts of the system and, importantly, on policy development and implementation, is necessary if ethico-political awareness is to develop.[16]

What to include in ethics education in professional programs, and its nature more generally, has been the subject of much debate; criticism has been made of its tendency to develop 'problem solvers' while ignoring the development of sensitivity and judgement.[24] Lawlor[25] has argued that abstract moral theories are often too difficult to apply in meaningful ways to real clinical problems during undergraduate education. Overarching moral theories constitute what the philosopher Raymond Geuss[26] has called the 'ethics first' approach. A political philosopher, Geuss argues against beginning with abstract notions of 'fairness' or 'justice' then moving from such abstract concepts to make normative political claims about what governmental policy ought to do (for instance). Instead he advocates starting from real situations, historically and socially located, in order to understand politics. While this anti-theoretical stance is a very different project to our task of educating professionals—who are of course bound by professional standards—the idea of beginning with 'real' practice offers new questions and rejects the imposition of ideological concepts which might bear no relation to students' experiences of healthcare practices. His criticism of these 'ethics first' approaches is that they fail to think about how and why we act in particular situations and deny the importance of power, when 'it is advisable to pay attention to it.' [26 (p 97)] By suspending, albeit experimentally, the overarching value claims made by health leaders, we might usefully look more thoughtfully at *how* and *where* health problems are managed, at *who helps* people live with illness or disability, and at the

ways in which health professionals and others contribute most effectively (or fail to do so).

Understanding how power manifests in healthcare relationships is intrinsic to ethical practice. The more nuanced work around values understands power to be inherent within relationships. By its nature it is interested in when values and interests conflict, and the ways in which power can be unequally distributed.

In similar vein, the principles that inform regulatory codes and other normative frameworks have a dual purpose, not only to guide and shape professional identity formation, but to identify when an individual falls below a standard.[27] This is fundamental to professions' ability to exert power over individuals in order to self-regulate and control membership. Being 'struck off' a professional register is career ending, yet paradoxically fear of such a possibility can lead to professional self-interest taking priority over patients' interests.

Understanding the power of organizations, formal and informal groups and teams, and how to utilize forms of power, is part of developing a sense of agency that extends beyond the individual. Such agency is described by Beckett as social, embodied, negotiated and performative in nature.[28] Kramer's[29] study showed how developing the ability to influence events, through greater understanding, knowledge and confidence, reduced the distress and conflict experienced by novices. A sense of being able to shape and influence events, with and alongside others, emerges as invigorating in exactly the same way that feeling helpless, isolated and pawn-like leads to listlessness and passivity. Viewed in this way, advocating on the part of a patient, or their family member or a work colleague, is not an act of 'compassion', but an act of solidarity.

Moral Agency and Ethical Self-Formation

The renewed emphasis on values and the personal characteristics of health professionals has been accompanied by plans to further embed and measure certain characteristics within healthcare university programs. Smajdor[30] presents a compelling case against this project, seeing as a flawed endeavor the aim to 'incentivize' such emotional responses as compassion, because doing so risks encouraging cynical forms of compliance. Research into moral development supports her skepticism. It is unsurprising that students—who are able to identify the socially desirable responses in written tests that seek to examine their moral imaginations and ethical principles—often fail to enact the principles that they espouse. In one study, those scoring highest on moral reasoning tests also scored highest for 'amorality.'[31] Furthermore, exposure to the vagaries of practice has been found to reduce students' moral standards and expectations[32] or leave them more confused about what constitutes 'right' and 'wrong' forms of action.[33]

While certain personal qualities are necessary to practice effectively—such as a concern for people and an interest in their doing well—these are generally intrinsically motivated. Seeking to elicit them using extrinsic motivators, for instrumental purposes, is likely to have perverse effects.

As a source of learning, then, inquiry processes can reveal just how difficult allocating moral responsibility can be, especially when poor communication, inadequate levels of training or supervision, and confusion around delegated responsibilities muddy the water. These kinds of inquiry reports can show us the ways in which accountability is contingent—in sharp contrast to the reassuring learning outcomes that package and describe ethics courses in higher education.

For students to feel confident in this more situated and reflective form of moral agency, their *own* values, beliefs and sense of identity need to be the starting point for developing as professionals. The sociologist Anthony Giddens[34 (p86)] suggests that in the modern world people are called upon to engage in 'reflexive projects of the self', where they pursue certain projects, styles, and modes of inhabiting the world. Giddens' notion can help us to think about students' reflexive projects of the self, and how ethics education might speak to them in this more intimate way.

To focus on ethical theories is to leave unanswered the question most often raised by students: what am I supposed to *do* if an issue is not clear-cut? Being told that every situation is unique, and that 'it depends', can feel like short change—especially if students have shared personal stories, concerns and feelings. Worse,

it may even be interpreted as anything goes, or imply that 'ethics' as a topic is irrelevant to life.

In contrast, learning about healthcare work in more general, global terms—the uncertainties, injustices, frustrations, as well as the successes and rewards—enables a professional, personal and collective identity formation that is influenced and altered in important ways by such knowledge. Giddens[34 (p86)] offers an example of what he calls the reflexive shaping of self-identity: "A black woman heading a single-parent household, however constricted and arduous her life, will nevertheless know about factors altering the position of women in general, and her own activities will almost certainly be modified by that knowledge".

In the same way, trying to analyze messy and partial clinical experiences in an ethics session can be frustrating and leave students feeling as if they have failed to convey *exactly* what was happening or explain why they are left with particular feelings.[35] Whereas viewing such experiences in light of the position of healthcare professionals in general—the effects of moral strain or the excitement of witnessing a successful intervention—can be helpful in connecting one's own endeavors to those of colleagues, to wider trends or to special interest groups. In this way, students' use of blogs and other kinds of social media can be viewed as reflexive and identity forming pursuits, that position and connect them as people in the world, with interests and membership of communities within and outside their healthcare work. However such collegiality needs to extend to a commitment to act with and alongside others if the rhetoric of the heroic individual is to be challenged.

Moral agency can be a fragile and fleeting experience, in need of active reinforcement if it is not to be subsumed by ideologies imposed from elsewhere. When student nurses and care workers blew the whistle on cruel practices taking place at Garlands Hospital in 1996, an internal inquiry criticized their lack of understanding of how practice in the 'real world' operated (and also blamed "the type of patient in this ward" as Butler and Drakeford[5] found to characterize so many inquiries).[36] Some knowledge and understanding of how corrupt, micro-political forces were diminishing strategic governance at that particular Trust through those years,[37] would have helped them to remain resilient and view themselves as moral agents, rather than as victims of an unjust system.

Ethical self-formation, described by Giddens[32] as a reflexive project of the self, offers us a way of thinking about how *education*—through its social and relational forms of learning—might combat the 'existential isolation . . . from the moral resources necessary to live a full and satisfying existence.'[32 (p9)] Such a sense of self is *actively shaped* by events over time and yet has an enduring dimension because of the self-conscious and reflexive ways in which persons shape their sense of who they are and how they act upon the world. Understanding how different forms of power operate both to *conceal*, in ways described by Epstein,[38] and to *sustain* such injustices offers a more constructive way of using distressing experiences as catalysts for action.

Summary

The central argument of the paper is that ethical practice requires health professionals to be effective moral agents. A more responsible form of moral agency, I want to suggest, requires an understanding of power: how it manifests in relationships, organizational cultures and structurally, and the ways in which it introduces risk and threatens safe practice. Such agency requires a sense of oneself, as intimately caught up in and influential upon the lives and wellbeing of others, as a part of communities and with interests and allegiances that transcend disciplinary and patient/professional boundaries. **Educators themselves, then, need a better understanding of the complexities of practice and its changing nature, in order to counteract the prevailing discourses that place compassion and other personal emotions and characteristics at the forefront of educational requirements.**

Firstly I argue that ethics education needs to reflect the many constituencies and perspectives, in order to prepare students for collaborative work—across disciplines, and with people who use health services as patients and carers. This is imperative given the increasingly complicated arenas in which healthcare takes place, with changing responsibilities and types of delegation in a more mixed economy of care.

Next, I contend that ethical practice takes place in politically informed arenas in which power is a key

feature of actions and decisions. Examining the nuances and complexities of why people act in certain ways is pertinent to understanding the boundaries of ethics and to extending them to include broader motives and plans. It is central to the case for change that while ethics education focuses predominantly on the more theoretical and abstract elements of moral philosophy, or promotes an ethics first approach, an opportunity is lost to view these messier, difficult and shared problems as moral ones that can be challenged.

Finally I suggest that ethics education has a role to play in supporting students to be fully involved as moral agents, influencing and being shaped by communities and individuals within society beyond the narrow clinical domains. This is in contrast to the contemporary project to inculcate particular values through healthcare education, with its risk of instilling a narrow and unsophisticated understanding of what constitutes ethical practice.

It is for this reason that the stance of the educator is proposed as pivotal to the success of such alternative approaches. Appreciation of the unique and situated ethical problems students encounter requires openness and a preparedness to engage with uncertainty. It requires a concerted commitment to improvement that crosses traditional demarcations and unifies, understanding such responses to promote resilience and to be more effective and sustainable than heroic individualism. It requires a willingness to explore new ideas, and to rehearse viewpoints, and ultimately to accept that confusion can be creative and is essential to transformative learning. Ethics education, conceived of in these ways, might look different and is likely to take place outside as well as inside the classroom. Interprofessional education and collaborative learning with patients and others offer ways to begin re-imagining how it might more directly support ethical practice.

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Hatherleigh's Note: Additional typeface treatment was added to text for emphasis. Supplementary title page information, CME, Best Practices, and medication trade names, if any, were also included. British English spelling was changed to US English.

Competing interests: The author declares that she has no competing interests.

Author's contribution: As the sole author of the paper JW was responsible its conception, design, drafting and writing. She is accountable for all aspects of the work including its accuracy and integrity.

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Multiple-Choice Questions

25. According to the author, poor standards of care:

A. are often reflected by supportive healthcare cultures.

B. can be reflected by an environment of fear where dysfunctional situations are alleviated rather than challenged.

C. reflect effective and safe governing mechanisms in practice.

D. None of the above

26. Moral strain:

A. is not prevalent among healthcare professionals.

B. is highly associated with work-related stress.

C. is highly associated with helplessness.

D. B & C

27. According to the author, which of the following topics is unlikely to be included in ethics education for healthcare professionals?

A. financial and resourcing decisions

B. contractual arrangements

C. workforce changes

D. All of the above

28. Which of the following is/are a central theme of this lesson?

A. Ethical practice requires health professionals to be effective moral agents.

B. Moral agency requires an understanding of power: how it manifests in relationships, organizational cultures and structurally, and the ways in which it introduces risk and threatens safe practice.

C. Educators need a better understanding of the complexities of practice and its changing nature in order to counteract the prevailing discourses that place compassion and other personal emotions and characteristics at the forefront of educational requirements.

D. All of the above

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Best Practices in CME

The Changing Landscape of Care: Does Ethics Education Have a New Role to Play in Health Practice?

By Julie Wintrup

ID#: L903350

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

CME Lesson Overview

This lesson proposes that ethics education has a new contribution to make, in supporting and promoting ethical practice—as it is defined in and by the everyday actions and decisions of practitioners and people who need health services.

Key Point 1: Effective Moral Agency

Moral agency, requires an understanding of power: how it manifests in relationships, organizational cultures and structurally, and the ways in which it introduces risk and threatens safe practice.

Key Point 2: Ethical Education Needs

Ethics education needs to reflect the many constituencies and perspectives, in order to prepare students for collaborative work—across disciplines, and with people who use health services as patients and carers.

Key Point 3: Contexts of Emerging Ethical Ideas

Ethical practice takes place in politically informed arenas in which power is a key feature of actions and decisions. Examining the nuances and complexities of why people act in certain ways is pertinent to understanding the boundaries of ethics and to extending them to include broader motives and plans.

Key Point 4: The Educator's Role

As educators, whether primarily in practice or academic roles, we have a responsibility to more thoroughly prepare healthcare students for the realities of professional practice in an increasingly mixed economy of care with its bureaucracy, visibility, increasing forms of delegation, marketization and complex regulatory and governance arrangements. Lines previously drawn around what is considered to be 'ethical practice' may need to be redrawn to include a more astute understanding of moral responsibility and delegation in such uncertain and rapidly changing contexts.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Effects of Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea on Cognitive Functions: Evidence for a Common Nature

Georgia Andreou, Filippos Vlachos, and Konstantinos Makanikas

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

KEY WORDS: COPD • Sleep Apnea Syndrome • Cognition • OSAS

LEARNING OBJECTIVES: This lesson provides an overview of *chronic obstructive pulmonary disease* (COPD) and *obstructive sleep apnea syndrome* (OSAS). Clinicians will review how patients suffering from these disorders show similar neurocognitive impairments. This lesson examines symptoms in COPD and OSAS and their impact on cognitive function.

LESSON ABSTRACT: Patients with *chronic obstructive pulmonary disease* (COPD) and *obstructive sleep apnea syndrome* (OSAS) show similar neurocognitive impairments. Effects are more apparent in severe cases, whereas in moderate and mild cases the effects are equivocal. The exact mechanism that causes cognitive dysfunctions in both diseases is still unknown and only suggestions have been made for each disease separately. The primary objective of this review is to present COPD and OSAS's impact on cognitive functions. Secondly, it aims to examine the potential mechanisms by which COPD and OSAS can be linked and provide evidence for a common nature that affects cognitive functions in both diseases. Patients with COPD and OSAS compared to normal distribution show significant deficits in the cognitive abilities of attention, psychomotor speed, memory and learning, visuospatial and constructional abilities, executive skills, and language. The severity of these deficits in OSAS seems to correlate with the physiological events such as sleep defragmentation, apnea/hypopnea index, and hypoxemia, whereas cognitive impairments in COPD are associated with hypoventilation, hypoxemia, and hypercapnia. These factors as well as vascocerebral diseases and changes in systemic hemodynamic seem to act in an intermingling and synergistic way on the cause of cognitive dysfunctions in both diseases. However, low blood oxygen pressure seems to be the dominant factor that contributes to the presence of cognitive deficits in both COPD and OSAS.

COMPETENCY AREAS: This lesson presents a review of the impact that COPD and OSAS has on cognitive functions. As individuals age, the prevalence of these disorders will likely increase. Clinicians will gain knowledge of presenting symptoms in COPD and OSAS, review treatments for the disorders, and better understand the possible mechanisms that may contribute to cognitive decline.

Introduction

Chronic obstructive pulmonary disease (COPD) and *obstructive sleep apnea syndrome* (OSAS) represent two of the most common chronic respiratory disorders. **COPD is characterized by airflow limitation that is not fully reversible, while OSAS by periodic complete or partial upper airway obstruction during sleep.[1, 2]** Studies have shown that the occurrence of both diseases among adults is advancing along with aging. As the global population ages, the prevalence of COPD and OSAS will increase in future and as a result more and more patients will be in need of health care.[1, 3] Furthermore, it has been suggested that COPD and OSAS affect cognitive functions.[4, 5] However, there are different opinions on which cognitive abilities are affected by these two respiratory disorders and on the exact cause of cognitive deficits. Comparing studies is difficult because of design study variability, differences in severity of disease, mode of selection of patients and control groups, sample size, and respective study inclusion and exclusion criteria and because of different criteria that are used to assess the severity of syndromes.[6, 7] Other variables such as the neuropsychological battery chosen, the treatment prescribed (e.g., oxygen supply), corticoid prescriptions,[6] and different group ages are also confounding factors.[8] Nevertheless, the present study is an attempt to compare the performance of COPD and OSAS patients in common neuropsychological tests according to severity so as to understand better the role of respiratory/lung disturbances, blood gas levels, and sleep

Chronic Obstructive Pulmonary Disease (COPD)

***Chronic obstructive pulmonary disease* (COPD) is a progressive disease characterized by the presence of airflow obstruction secondary to emphysema or chronic bronchitis.[9]** COPD does not cause a fully reversible airway limitation due to chronic inflammatory process in the pulmonary tissue that often results in breathlessness for the patients, cough,[10, 11] and excessive mucus production.[12, 13] **In the United States, COPD is the fourth leading cause of death,[13] after heart disease, cancer, and stroke,[14] whereas its prevalence increases with aging.[15, 16]** The occurrence of COPD in general population is between 2.83%[15] and 6.9%,[17] while in ages older than 35 years old this percentage amounts to 17.4% in developed countries.[16] **More COPD patients are between their fifth and sixth decade of life[10] and there is a higher incidence of the disease among males than females.[16, 18]**

Tobacco smoking is the major cause of the disease, although only a minority of smokers develop clinically significant symptoms.[10] Other factors, such as indoor and outdoor air pollution, infection in childhood, asthma, genetic factors[1, 9] and occupational dust have been reported to contribute to the development of COPD.[10] COPD is associated with an increased mortality and morbidity implications such as lung cancer, anemia,[10] pulmonary hypertension, polycythaemia, peripheral oedema, cardiovascular complications, obstructive sleep apnea, chronic infections, and musculoskeletal disorders (e.g., osteopenia and muscle atrophy)[1, 19] as well as nutritional depletion that is caused by increased metabolism during breathiness episodes.[11, 13] Patients with COPD are significantly more likely to report symptoms such as insomnia and difficulty in initiating and maintaining sleep.[20] Moreover, they have a higher rate of depression and anxiety compared to general population.[21] COPD has also been associated with reduced patients' quality of life due to restriction of activities and limitation of social life.[22]

The treatment of COPD patients is based on a combination of bronchodilators, corticosteroids, antibiotics, and mucolytics which have been found to improve lung functions, COPD symptoms and morbidity and mortality caused by extrapulmonary effects. Drug use has also been found to reduce exacerbation rates (major changes in patient's symptoms or their requirement for drug therapy) and the length of hospital stay.[11, 12] Furthermore, it has been found that drugs improve patients' quality of life[11] and mood.[23] However, the most effective treatment is smoking cessation which delays disease progression[11] or returns lung functioning to normal, if COPD is diagnosed at early stages.[12] Some other kinds of treatment such as pulmonary rehabilitation, *lung volume reduction surgery* (LVRS),[10] *long-term oxygen therapy* (LTOT),[12] and *continuous positive airway pressure* (CPAP)[14] are also effective in reducing patients' morbidity and mortality.

Definition:

COPD is determined on the basis of chronic respiratory symptoms, including irreversible airflow limitation associated with dyspnea and particularly with exertion, productive cough, and wheeze.[11, 14] The pathological processes in COPD include inflammatory damage of the large airways (trachea, bronchi) and small airways (bronchioles) and often alveolar dysfunction of small airways.[12, 13] The glandular hypertrophy and the reduced number of cilia that are observed in large airways cause increased cough.[12] However, the majority of symptoms in COPD patients is based on the reduced ability of lungs to empty sufficiently. Inspiratory muscle weakness, lung hyperinflation, and increased ventilatory demand relative to capacity contribute to the presence of dyspnea.[12, 24] On the other hand, alveolar dysfunction causes impairment in gas exchange (hypoventilation) and ventilation-perfusion mismatching, which result in hypoxemia and hypercapnia.[12, 25]

The diagnosis of COPD is based on a typical history of persistent and progressive symptoms on risk factors for COPD and on assessment of physiologic measures of lung function.[12] The most commonly used test for the evaluation of lung dysfunction is spirometry.[10] The severity of the disease is based on spirometric criteria measuring the *forced expiratory volume in 1 sec* (FEV_1) and the ratio of FEV_1 to *forced vital capacity* (FVC) after bronchodilator administration.[1, 11] The stage of severity of COPD is determined according to 2010 *Global initiative for Obstructive Lung Disease* (GOLD) guidelines. Therefore, COPD is categorized as mild when FEV_1 is ≥80%, moderate when FEV_1 is among ≤50–<80%, severe when FEV is ≤30%–50%, and very severe when COPD patients are presented with an FEV_1 <30%. Diagnosis also demands FEV_1/FVC to be <0.70.[1, 26] A useful feature for confirmation of the diagnosis is that COPD patients' lung functions do not return to normal after bronchodilator administration, in contrast to patients with other breathing disorders (e.g., asthma).[12]

Severity of hypoxia in COPD is defined by blood oxygen levels. A mild stage of severity is considered the one with an oxygen partial pressure (PaO_2) between 50 mmHg and 80 mmHg.[27] At this level, there is complete compensation and general function is barely altered. Oxygen partial pressure between 35 and 50 mmHg is generally considered moderate hypoxia, a state which leads to a negative impact on cognition. Finally, when PaO_2 is below 35 mmHg the hypoxia is considered severe.[6] As regarding hypercapnea, it is characterized as abnormal when carbon levels exceed the normal range of 35 mmHg to 45 mmHg.[27]

Effects of COPD on Cognitive Functions:

Chronic obstructive pulmonary disease has been found to cause a general cognitive decline[28, 29] especially in cognitive functions such as attention, psychomotor speed, memory and learning, visuospatial and constructional abilities, executive functions, and language skills[28, 30] A summary of relevant studies and their results is presented in Table 1.

Attention

Attention in COPD patients is one of the most widely studied cognitive functions. Impairments on vigilance and sustained visual attention have been documented by several studies.[31-33] More specifically, a study showed that severe-to-very severe COPD patients with mild hypoxia performed poorly on visual sustained and selective attention tasks.[34] Other studies have proved that severe COPD patients with mild-to-moderate hypoxia performed poorer than healthy controls on alerting, orienting tasks, and sustained attention tasks.[35-37] Attention decline has also been observed in severe COPD patients with moderate hypoxia and hypercapnia.[38]

Moreover, a research on moderate and severe COPD patients with mild severity oxygen pressure and moderate severity nocturnal oxygen desaturation found impairments in selective and sustained attention.[39] Poor performance in attention tasks has been demonstrated even in nonhypoxemic severe COPD patients.[40, 41]

On the other hand, there are studies on COPD patients which found a mild decline in attention abilities[42] and an intact visual immediate attention even in severe COPD patients.[43] A more recent study on severe COPD patients who were mildly hypoxemic noted that the prevalence of visual and verbal attention decline was 14.9% and 2.2%, respectively.[44] Overall, the aforementioned studies have demonstrated that COPD patients exhibit poorer performance than healthy controls in several domains of attention.

Table 1:
Studies Examining the Effect of COPD on Cognitive Functions

Study	Sample characteristics	Type of study	Results
Crews et al. 2001[9]	47 patients, (FEV_1) < 25% age = 55.45 ± 6.67	Case control—normative study	50% of the patients exhibited impaired memory performance. Clinically notable frequencies of impairment (greater than 20%) were found on language abilities, executive functions, and psychomotor speed.
Antonelli-Incalzi et al. 2007[28]	149 patients, FEV_1 = 36.6 ± 17.8%, age = 69.3 ± 8.5	Clinical case—normative study	Patients exhibited a general cognitive decline.
Hung et al. 2009[29]	4150 patients, 29% severe (oxygen depended or disease related activity limited), age = 62.6 ± 1.8; 71% nonsevere, age = 62.9 ± 1.8	Community sampled case—control study	Only severe COPD was associated with lower cognitive performance
Etnier and Berry 2001,[30]	98 patients, age = 58–80, FEV_1 = 58.34 ± 16.41%	Exercise intervention follow-up study	Age, aerobic fitness, or pulmonary function are predictive of cognitive performance on fluid intelligence, reaction time, and working memory span.
Borak et al. 1996[31]	90 patients (severe COPD treated with long-term oxygen therapy)	Clinical case study	Patients presented poor visual, verbal, and spatial memory.
Kozora et al. 2002[32]	30 patients, age = 66.5, FEV_1 = 39.9 ± 1.6%	Clinical case—control study	Significant impairment in visual attention, verbal memory, constructional abilities, psychomotor speed, and executive functions.
Kozora and Make 2000[33]	30 patients (severe COPD, followed 3 weeks of rehabilitation), 29 untreated COPD patients, 21 healthy controls	Clinical case—control study	Significant group differences were found on sustained visual attention, visual memory, and language abilities.
Vos et al. 1995[34]	39 patients, age = 65.9 ± 5, FEV_1 = 33 ± 10%, 38 healthy controls	Case—control study	Lower attention performance of COPD patients in comparison to healthy controls.
Klein et al. 2010[35]	60 patients, age = 63.2 ± 9.8 FEV_1 = 36.4 ± 12.5%, 60 healthy controls	Clinical case—control study	Significant group differences found in phasic alertness and orienting but not in executive attention. Reaction time was significantly slower in the COPD group. Differences were found in verbal, visual learning, and logical thinking.
Emery et al. 2001[36]	29 patients, age = 67.8 ± 7.4, FEV_1 = 43 ± 17%, 29 controls	Clinical study of exercise effects	Only the improved performance in verbal fluency test was associated with exercise.
Kozora et al. 2005[37]	39 patients, age = 64.8 ± 4.9 FEV_1% = 24.9 ± 11, 39 healthy controls	Clinical case—control study	Patients with moderate-to-severe emphysema had impaired attention, verbal memory, and constructional abilities.
Watanabe et al. 2001[38]	1 patient, 71 yrs old, FEV_1 = 39%	Clinical case study of lung volume reduction surgery	All cognitive functions improved after lung volume reduction surgery.
Orth et al. 2006[39]	32 patients, age = 57,4 ± 8,2 FEV_1 = 50,4 ± 18,2%, 10 healthy controls	Clinical case—control study	Patients demonstrated significantly worse results than healthy controls in intelligence, simple, selective, and sustained attention tasks.
Antonelli-Incalzi et al. 2003[40]	15 patients (COPD with severe hypoxemia), 18 (COPD without hypoxemia), 10 healthy controls	Clinical case—control study	Patients performed below normal in verbal attainment, attention, and deductive thinking tasks.
Ortapamuk and Naldoken 2006[41]	8 patients (COPD with hypoxemia and hypercapnia), age = 52.6 ± 5.4, 10 patients (with stable COPD), age = 54.8 ± 6.9, FEV_1 = 33.9 ± 13%, 10 healthy controls	Clinical case—control study	Scores in verbal memory, delayed recall, and attention tasks were significantly lower in COPD patients than healthy controls. No differences in psychomotor speed.
Kozora et al. 1996[42]	32 patients (COPD with mean partial arterial oxygen pressure 68.8 mm Hg, 73% receiving supplementary oxygen), age = 70.3, 31 healthy controls	Clinical case—control study	COPD patients performed significantly worse than controls in verbal fluency and attention tasks.

Study	Sample characteristics	Type of study	Results
Incalzi et al. 1993[43]	36 patients (severe COPD, receiving oxygen therapy), age = 69 ± 10, 29 normal adults (69 ± 7 yr), 20 normal elderly adults (78 ± 2 yr), 26 patients (Alzheimer-type dementia, (72 ± 2 yr), 28 patients (multi-infarct dementia, 70 ± 8 yr)	Clinical case—control study	48.5% of patients with COPD had a specific pattern of cognitive deterioration characterized by impairment in verbal and verbal memory tasks, well-preserved visual attention, and diffuse worsening of the other functions.
Antonelli-Incalzi et al. 2006[44]	149 patients, age = 68.7 ± 8.5, FEV_1 = 36.5 ± 18.0%	Clinical case study	The prevalence of cognitive impairment was 32.8%. Visual memory was not impaired.
Borson et al. 2008[45]	18 patients (mild to severe COPD), 2 patients (FEV_1 = 50–79%), 8 patients (FEV_1 = 30–49%), 8 patients (FEV_1 < 30%), age = 68.5 ± 8.0, 9 healthy controls	Clinical case—control study	Performance in verbal memory, land psychomotor speed was impaired.
Liesker et al. 2004[46]	30 patients, FEV_1 = 49 ± 8% age = 64.8, 20 controls	Clinical case—control study	COPD patients performed significantly worse than controls in psychomotor speed tasks.
Stuss et al. 1997[47]	18 patients FEV_1 = 74 ± 30%, age = 66.4 ± 7.6	Clinical case—control study	Intelligence scores and psychomotor speed and memory abilities were within average range.
Antonelli-Incalzi et al. 2009[48]	54 patients (hypoxemic COPD), age = 68.8 ± 9.0, FEV_1 = 36.9 ± 16.5%	Clinical study	Patients had impaired performance in copying drawings with landmarks
Incalzi 1997[49]	42 patients (COPD with hypoxemia and hypercarbia), FEV_1 = 34 ± 9%, age = 70 ± 9.7, 27 normal subjects, 31 patients (Alzheimer's disease), 26 older normal subjects	Clinical case—control study	The overall cognitive performance of COPD patients was significantly inferior to that of the rest of the groups. Both passive recognition and active recall of learned material were severely impaired in COPD patients.
Fioravanti et al. 1995[50]	50 patients	Case study	30% of COPD patients had impaired immediate verbal memory.
Kozora et al. 1995[51]	40 patients, age = 64, 40 healthy controls	Clinical case—control study	COPD patients were significantly impaired during copying.
Kozora et al. 1998[52]	59 patients, age = 66.7, 31 healthy controls, age = 65.9	Clinical case—control study	COPD patients performed significantly worse than controls in two tasks (verbal fluency and digit span) but not at a clinically impaired range.

Psychomotor Speed

A decline in psychomotor speed was evidenced by a variety of research studies. It has been shown that 26% of a group of very severe COPD patients with mild hypoxia were impaired in psychomotor speed.[9] Another study on severe COPD patients with mild-to-moderate hypoxia proved that they achieved statistically significant low scores in time reaction tests.[35] Furthermore, it has been shown[45] that severe COPD patients who were oxygen and non-oxygen dependent exhibited poor performance in psychomotor speed tests. This finding was consistent with the findings of a study[46] in which nonhypoxemic severe COPD patients had low performance in a psychomotor speed test. On the other hand, other researchers found[47] that moderate COPD patients, with mild hypoxia, performed within average range in a test which assesses psychomotor speed. Finally, there is a study[41] which failed to document differences between healthy controls and hypoxemic or nonhypoxemic patients in psychomotor speed tests. Up to now research has yielded contradicting data on the association of COPD and psychomotor skills. Therefore, more research is needed in order to shed light on the impact of COPD on psychomotor skills.

Memory and Learning

Memory dysfunctions are common in COPD patients. The majority of researchers have documented deficits in verbal short-term and long-term memory,[32, 41] in visual memory,[33] and in spatial memory.[31]

Severe-to-very severe COPD patients have usually been presented with a significant short-term verbal

memory decline. COPD patients' performance in visual span tests was found impaired in contrast to their performance in immediate visual memory tests which was found intact.[48] There is also a study[38] which has documented a verbal memory decline in a patient with severe COPD and moderate hypoxia, who was in need for lung volume reduction surgery. In patients with severe COPD and mild-to-moderate hypoxemia statistically significant differences in verbal and visual learning have been found when compared to healthy controls.[35] A research in severe COPD patients has documented impairments in delayed verbal memory.[37] In addition, poor performance in verbal memory and delayed recall was observed in nonoxygen and oxygen dependent patients with severe COPD[41, 45] although a decline in immediate visual memory was rarely found.[41, 44]

Some other studies have reported memory impairments in a significant percentage of COPD patients of their samples. It was found[49] that 80% of patients with severe COPD and mild-to-moderate hypoxia performed poorer than healthy controls in verbal short-term and long-term memory tests, while 38.1% of them presented a specific verbal memory profile. Another study[9] found that 50% of very severe patients with mild-to-moderate hypoxia had impaired immediate memory and 44% of them had difficulties in their long-term retrieval ability. A specific pattern of cognitive deterioration was found in 48% of patients with COPD, which included a dramatic verbal memory decline.[43] A recent study on severe COPD patients with mild hypoxia found that 37.3% of them was impaired in terms of short-term memory and 26.1% obtained low scores in long-term memory tests.[44] In another study,[50] it was noted that 30% of COPD patients had impaired memory which was confined to immediate verbal memory.

Finally, there is a number of studies that failed to document any memory deficits in COPD patients. Moderate COPD patients' performance with mild hypoxia was found within average normal range in memory tests,[47] while another study[39] on moderate COPD patients with mild oxygen blood pressure did not demonstrate notably poor scores in verbal learning memory tests. Moreover, short-term and long-term verbal memories have been found within normal range in nonhypoxemic severe COPD patients.[46, 48] Based on the discrepancy among the results of the aforementioned studies the issue of learning and memory abilities in COPD patients should be further examined in combination with the severity of hypoxia that these patients display because it seems that hypoxia has a negative impact on memory and learning.

Visuospatial and Motor Constructional Abilities

A decline in constructional abilities is very common among COPD patients.[32] Severe COPD patients with mild hypoxemia have been presented with impaired constructional abilities.[37, 51] Another study has noted a decline in visuoconstructional abilities in 40.3% of severe COPD patients with mild hypoxia.[44] On the other hand, there are researches in which a normal performance was found in hypoxemic and nonhypoxemic COPD patients[41] as well as in severe-to-very severe COPD patients with mild hypoxia.[48] Despite the slight discrepancy among the findings of studies on the impact of COPD on visuospatial and motor constructional abilities, most of them provide evidence for impaired visuoconstructional abilities in COPD patients.

Executive Functions

The presence of executive dysfunctions among COPD patients is still equivocal. There have been studies that found impairments in problem solving ability, abstraction abilities, and deductive thinking.[40] More specifically, studies on severe-to-very severe COPD patients with mild hypoxia have demonstrated mild impairments in executive functions.[37] A research on severe COPD patients with mild-to-moderate hypoxia showed impairments in logical thinking but not in general executive functioning.[35] A study[52] on severe COPD patients with mild hypoxemia also found a mild decline in letter fluency; however, this was not at a clinically impaired range. Concerning nonhypoxemic severe COPD patients, their performance in tests that assess mental flexibility was found poor.[46] Another study[47] found that moderate COPD patients' performance with mild hypoxia in tests that require mental shift ability was below average. It was also found[9] that 31% of very severe COPD patients with mild-to-moderate hypoxia exhibited impaired performance in tests measuring executive functioning. In addition, in a group of mildly hypoxemic patients

with severe COPD, it was noted that 40.3% of them performed poorly in copying complex drawings and 11.2% in Raven progressive matrices, a test examining nonverbal reasoning.

Nonetheless, there has been research, though limited, that either failed to find any significant poor performance in executive functioning in severe COPD patients with mild hypoxia[48] or noted that COPD patients' performance was similar to controls in executive functioning tests.[41] It must be stressed, however, that most studies support the notion that COPD is usually associated with executive dysfunctions.

Language Abilities

There has been a significant number of studies that have documented serious language impairments assessed with verbal fluency tests in COPD patients.[33, 36] A recent study found a language decline in nonhypoxemic and hypoxemic COPD patients in selected tests of verbal attainment.[40] Another study found that 48% of severe COPD patients presented a specific pattern of cognitive deterioration which included a dramatic decline in verbal fluency.[43] On the other hand, there is a research which has shown that only 10.4% of severe COPD patients with mild hypoxia showed sentence construction decline and 7.5% a verbal fluency impairment.[44]

Nonetheless, the presence of language dysfunctions in COPD patients is still controversial. There is a study which found that severe COPD patients with mild hypoxia performed low in verbal fluency tests, although this was not at a clinically impaired range.[52] Similarly, it was demonstrated[47] that moderate COPD patients with mild hypoxia performed within average range in the aphasia screening test, while in a verbal fluency test their performance was towards the low end of the average range.

Moreover, a study[9] on very severe COPD patients with mild-to-moderate hypoxia found normal scores in vocabulary tests. It has also been shown that severe COPD patients' performance in crystallized intelligence (knowledge and vocabulary)[35] and in language (verbal fluency, sentence construction) was within normal range.[48] Finally, there is a research[41] which reported that hypoxemic and nonhypoxemic COPD patients' performance was similar to controls in verbal production and verbal competence tests. From the aforementioned studies (for details see Table 1) it is apparent that the unclear association of COPD and language abilities can be partially attributed to differences in the severity of disease, mode of selection of patients and control groups, and on different criteria that are used to assess the severity of syndromes.

Obstructive Sleep Apnea-Hypopnea Syndrome

Obstructive sleep apnea syndrome **(OSAS) is part of a spectrum of sleep related breathing disorders which also includes *central sleep apnea* (CSA) (apnea without respiratory effort), mixed sleep apnea (episodes of obstructive sleep apnea and central sleep apnea), upper airway resistance syndrome (increased respiratory effort without apnea or hypopnea), and snoring.[3, 53]** It affects 2% of women and 4% of men in middle age adults.[54] A recent study on a population-based sample of subjects aged 30 to 70 years found that 19% of men and 15% of women present hypopnea and apnea episodes above normative index.[55]

OSAS is characterized by a perturbation of the pharyngeal dilator muscles. More specifically, it occurs when the muscles relax during sleep, causing soft tissue in the back of the throat to collapse and block the upper airway and it is associated with or without faulty upper airway anatomy such as macroglossia, hypertrophy of tonsils, and long uvula.[2, 3] **Other risk factors that enhance the probability of OSAS are obesity, increased neck circumference, positive family history, male postmenopausal status, Down syndrome, Pierre-Robin syndrome, alcohol consumption before bedtime, tobacco and hypnotics use, and sleeping in supine position.[2, 56] These factors result in episodes of complete or partial upper airway obstruction during sleep and in increased sleep arousals that terminate the apneic episodes. These disturbing events while sleeping cause decreased oxygen saturation as well as sleep fragmentation.[3, 57]** It has been found that stage 2 of sleep increases, while stage 1, stage 3, stage 4, and REM sleep decrease in OSAS,[3, 56] although there are different opinions on the decreased total time of REM sleep.[58, 59] This abnormal sleep architecture makes sleep lighter and less restorative.[56]

The most well-known symptom of obstructive sleep apnea/hypopnea syndrome is excessive daytime sleepiness,[60] although some studies failed to report daytime somnolence.[61] Daytime sleepiness is usually assessed with *Multiple Sleep Latency Test* (MSLT), *Maintenance of Wakefulness Test* (MWT), and with a series of questions included in the *Epworth Sleepiness Scale* (ESS) which evaluate patients' condition in common everyday situations.[62] The majority of patients with OSAS report that they fall asleep in quiet and monotonous situations such as watching television, reading a book, or driving a vehicle.[56] Fatigue, nonrefreshing sleep, insomnia, loud snoring, gasping, choking, and reports of breathing interruptions by bed partner are common daytime and nocturnal symptoms of sleep apnea.[63] Poor quality of life, poor interpersonal relationships, and low work and school efficiency have been observed in OSAS patients.[5] **Moreover, patients with OSAS have a high frequency of psychopathology such as depression and hypochondriasis.[64]** In addition, patients with OSAS present increased morbidity due to high rates of cardiovascular diseases and hypertension[65] as well as increased mortality.[5]

The treatment of OSAS is based on restoring the upper airway flow. For that reason, the most effective treatment for patients with craniofacial abnormalities is surgical treatment. In the rest of OSAS patients the most effective treatment is the *continuous positive pressure therapy* (CPAP) which consists of an air pressure generating device and a fitting mask that is applied over the nose or the mouth of the patient. The positive air pressure maintains upper airway patency and prevents upper airway obstruction, while the patients are asleep.[2, 3] CPAP therapy has been shown to improve nocturnal breathing, oxygen saturation,[3] and mean blood pressure.[66] As a result, it decreases hypertension and the risk of cardiovascular and cerebrovascular events.[65] CPAP therapy in most cases decreases daytime sleepiness[64] and improves OSAS patients' mood[67] and quality of life.[68] However, these positive effects have not always been reported.[61]

Recent studies have shown that CPAP treatment is also related to cognitive improvements.[69] In a clinical review,[56] it has been concluded that CPAP is effective in reducing symptoms of sleepiness and improves some cognitive functions.

Definition:

Obstructive sleep apnea syndrome (OSAS) is defined as an obstruction of airflow for 10 seconds or longer, while both apneas and hypopneas are observed in the syndrome. Apnea is characterized by the cessation of airflow (decrements in airflow of ≥90%) for 10 seconds or more.[2, 3, 53] On the other hand, hypopnea is usually characterized by a reduction of ≥30% in airflow for 10 seconds associated with a ≥3% decrease in oxygen saturation or arousal.[70] According to the American Academy of Sleep Medicine, hypopnea is defined as a decrease of ≥30% in airflow, for a period lasting at least 10 seconds, followed by ≥4% oxygen desaturation, while at least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea.[2, 71] The diagnosis of the syndrome is based on daytime and nocturnal symptoms and especially on a full-night polysomnogram,[72] which includes electroencephalographic, electro-occulographic electromyographic, oxygen saturation, oral and nasal airflow, respiratory effort, and electrocardiographic and leg movement recordings.[2] OSAS severity is defined according to *apnea-hypopnea index* (AHI), by calculating the sum of apneas plus hypopneas per hour of sleep. According to *apnea/hypopnea index* (AHI), OSAS patients are divided into 3 groups of severity: mild OSAS (AHI ≥ 5), moderate OSAS (AHI = 15–30), and severe OSAS (AHI ≥ 30).[2]

Neurocognitive Deficits in Obstructive Sleep Apnea/Hypopnea Syndrome:

It has been repeatedly documented that OSAS has a negative impact on a wide range of cognitive functions. Attention, memory, psychomotor speed, visuospatial abilities, constructional abilities, executive functions and language abilities are among the most impaired cognitive domains in OSAS patients.[5, 73] A summary of relevant studies is presented in Table 2.

Table 2:
Studies Examining the Effects of OSAS on Cognitive Functions

Study	Sample characteristics	Type of study	Results
Quan et al. 2006[7]	67 patients, age = 59.4 ± 9.2, AHI = 22.4, AHI > 10, 74 healthy controls	Case—control study	Mild to moderate OSAS has little impact on the selected measures of attention, executive function, and motor and processing speed.
Mathieu et al. 2008[8]	28 patients, two age groups, Group A: <50 yr, AHI = 50.8 ± 4.1, Group B: >50 yr, AHI = 42.5 ± 4.1, 30 healthy controls	Case—control study	OSAS patients exhibit attention and verbal long-term memory dysfunctions. Short-term memory, working memory, and planning and flexibility appeared well preserved. OSAS patients showed some difficulty in the initial acquisition of the procedural skill but no procedural skill-learning deficit over time.
Lim et al. 2007[53]	46 patients; 14 patients (OSAS treated with placebo), age = 48.9 ± 3.2, AHI = 65.8 ± 8.2; 17 patients (OSAS treated with CPAP), age = 46.7 ± 2.4, AHI = 63.5 ± 7.8; 15 patients (OSAS treated with oxygen), age = 47.1 ± 2.3, AHI = 58.6 ± 8.3	Randomized placebo—controlled design	OSAS patients showed diffuse impairments, particularly in terms of speed of information processing, attention and working memory, executive functioning, learning and memory, and alertness and sustained attention.
Yaouhi et al. 2009[58]	16 patients, age = 54.75 ± 5.71, AHI = 38.31 ± 14.33, 14 healthy controls	Case—control study	Patients showed poor performance on episodic memory. The remaining neuropsychological test scores (attention, vigilance, working memory, executive functions, and verbal fluency) were within the normal range.
Ferini-Strambi et al. 2003[60]	23 patients, age = 56.5 ± 6.13, AHI = 54.9 ± 13.37, 23 healthy controls.	Case—control study	OSAS patients had a significant impairment, compared to controls, in tests of sustained attention, visuospatial learning, executive function, motor performance, and constructional abilities.
Muñoz et al. 2000[64]	80 patients, age = 49.1, AHI = 60.2, 80 healthy controls	Clinical study of CPAP effects	Patients had a longer reaction time and poorer vigilance than healthy controls.
Engleman et al. 1994[67]	32 adult patients, AHI = 28 (range 7–129)	Placebo—controlled, crossover study	Patients showed improved vigilance, mental flexibility, and attention after CPAP treatment.
Engleman et al. 1999[68]	34 patients, age = 44,8 ± 6, AHI = 10 ± 3 (range 5–15)	Placebo control study of CPAP effects	Differences between before CPAP and after CPAP treatment in OSAS patients in attention (improvement in tests such as digit symbol examining attention skills).
Naegele et al. 1998[69]	17 patients, age = 44.80 ± 2.5, AHI = 53.5 7.6, 17 healthy controls	Case—control study of CPAP effects	Executive and learning disabilities as well as short-term memory impairment were found in OSAS patients.
Andreou and Agapitou 2007[73]	20 adolescents, age = 18.41 ± 0.37, AHI = 15.48 ± 7.08, 20 healthy controls	Clinical case—control study	Snoring adolescents showed reduced language and verbal abilities which were associated with disruption of sleep by apneas.
Aloia et al. 2004[74]	37 peer-reviewed articles were selected for this review	Review	Findings were equivocal for most cognitive domains. Treatment was noted to improve attention/vigilance in most studies but not constructional abilities or psychomotor functioning.
Rouleau et al. 2002[75]	28 patients, 18 healthy controls	Clinical study	OSAS patients did not show procedural skill learning deficits and episodic memory impairments. Frontal dysfunction, decrement in psychomotor efficiency, and vigilance characterized the impaired neuropsychological profile of OSAS patients.
Lau et al. 2010[76]	37 adult patients (moderate to severe OSAS treated with CPAP) 27 healthy controls	Clinical case—control study	Treated individuals performed at a comparable level to controls on basic working memory storage tests but showed a significant reduction on tests of working memory, requiring central executive functioning. The patients also performed worse on complex attention, executive function, and psychomotor speed tests than healthy controls.

Study	Sample characteristics	Type of study	Results
Kingshott et al. 2000[77]	62 patients, age = 51 ± 11, AHI 62 ± 33	Clinical case study of CPAP treatment	Cognitive performance tests measuring coding speed, reaction time, and attention were found improved after CPAP therapy.
Mazza et al. 2005[78]	20 patients, age = 51 ± 2 yrs, AHI = 45 ± 22, 40 controls	Clinical case—control study	95% of patients had vigilance and/or attention impairment.
Pierobon et al. 2008[79]	157 patients, age = 47.8 ± 11.9, AHI = 54.4 ± 0.9	Clinical case—normative study	Patients were impaired in short-term verbal memory and in short-term visual spatial memory. 40.8% did not have cognitive deficits.
Monasterio et al. 2001[80]	142 patients, age = 53 ± 9 AHI = 10–30	Clinical case—control study	All the initial mean values of the cognitive tests performed were not impaired.
Twigg et al. 2010[81]	60 patients, age = 51 ± 9, AHI = 23.1, 60 healthy controls.	Clinical case—control study	Patients with OSAS displayed reduced performance on verbal episodic memory tasks, whereas visual episodic, semantic, and working memory remained intact.
Dècary et al. 2000[82]	Review	Review	Poor general intellectual functioning, attention, memory and learning abilities, executive functions, and motor performance were found in OSAS patients.
Felver-Gant et al. 2007[83]	56 patients, age = 52.8 ± 11.2, AHI = 41.4 ± 22.1	Clinical case—control study	Working memory, declarative memory, executive functioning, and motor speed was impaired in OSAS patients.
Daurat et al. 2008[84]	28 patients, 29 healthy controls	Clinical case—control study	Recollection was strongly disturbed in patients, while attention was only slightly disturbed.
Aloia et al. 2003[85]	12 patients, age = 64.8 ± 6.4, AHI = 51.2 ± 19.8	Clinical case study	Attention, verbal delayed recall, constructional abilities, and language were impaired in OSAS patients.
Feuerstein et al. 1997[86]	10 patients, 10 healthy controls	Clinical case—control study of CPAP treatment	Patients were found with a significant decreased ability to initiate new mental processes and to inhibit automatic ones in conjunction with a tendency for perseverative errors. Deficits of verbal and visual learning abilities.
Lee et al. 2009[87]	30 patients, 30 healthy controls	Clinical case—control study	More severe cases of OSAS were associated with impaired language function reflecting frontal-subcortical pathology.
Grenèche et al. 2011[88]	12 patients, age = 51.8 ± 2.5, AHI = 58.9 ± 11.4, 10 healthy controls	Clinical case—control study	OSAS patients exhibited poor working memory performances. Immediate memory was not impaired.
Torelli et al. 2011[89]	16 patients, age = 55.8 ± 6.7, AHI = 52.5 ± 26.0, 14 healthy controls	Clinical case—control study	Patients with OSAS had impaired auditory-verbal learning. No other significant differences between the two groups were detected.
Saunamäki et al. 2009[90]	40 patients, age = 47.2 ± 7.8, AHI = 41.0 ± 22.8; 20 healthy controls.	Clinical case—control study	Patients showed poorer performance than controls on executive functions.
Bardwell et al. 2001[91]	36 patients, Group A (placebo group), age = 48 ± 2.2, AHI = 43.6 ± 6.4, Group B (CPAP), age = 47 ± 1.9, AHI = 56.8 ± 5.4	Clinical study of CPAP effects	OSAS patients exhibited poor executive functions.
Salorio et al. 2002[92]	28 patients, age: 28–60 yrs, 24 healthy controls	Clinical case—control study	Patients exhibited poorer recall abilities across learning trials, less efficient use of semantic clustering, and poorer use of semantic cues. Retention of previously encoded information and recognition was intact. No deficits in general executive control.
Lis et al. 2008[93]	20 patients, age = 53.4 ± 10.5, AHI = 57.9 ± 20.2; 10 healthy controls	Clinical case—control study	Deficits in tasks of executive functioning.
Beebe et al. 2003[94]	25 studies. 1092 patients, 899 healthy controls.	Meta-analytic review of research through 2001	OSAS was found to have a negligible impact on intellectual and verbal functioning but a substantial impact upon vigilance and executive functioning. Data were mixed with regard to visual and motor functioning. Post-hoc inspection of the data suggested that tests of fine-motor coordination or drawing were more sensitive to OSAS than were tests of fine-motor speed or visual perception. Data were also mixed with regard to memory functioning.

Attention

Patients with OSAS have been found with impaired attention abilities[68] and more specifically with a decline in vigilance[74, 75] and in complex attention.[76] Research has shown that severe OSAS patients are characterized by diffused impairments in vigilance,[53, 60, 64] in selective and sustained attention as well as alertness.[53, 77] In line with the above studies, another study[8] showed that a group of patients with severe OSAS, when compared to controls, had poor performance in tests measuring sustained attention and vigilance. Moderate and severe OSAS patients have been found to show diffused impairments in vigilance,[67] as well as in selective, sustained, and divided attention.[78]

On the other hand, there have been studies on moderate and severe OSAS patients that failed to find deficits in attention.[58, 79] Moderate OSAS patients (AHI = 20 ± 6) performed at a normal range in neuropsychological tests that assess sustained, divided attention and vigilance.[80]

However, a study on mild-to-severe OSAS patients did not document a significant attention deficit on their part.[81] Additionally, other studies[7, 68] found no significant impairments in attention in mild and moderate OSAS patients, compared to healthy participants. From the findings of the aforementioned studies it is apparent that the association between OSAS and attention abilities is unclear, probably related to methodological differences across studies.

Psychomotor Speed

There are a significant number of studies[75, 76, 82] which have reported deficits in psychomotor efficiency among OSAS patients. A study[53] which compared normative data to severe OSAS patients' performance in psychomotor tasks found a decline in psychomotor speed. There has also been evidence for psychomotor speed deficit in moderate and severe OSAS patients.[58, 83]

However, differences among severe OSAS patients' and healthy controls' performance in psychomotor speed tests have not always been detected.[8] In a recent study,[81] psychomotor deficits in mild-to-severe OSAS patients were not reported. In the same line, a study on patients with mild and moderate OSAS compared to controls did not show any significant poor performance in psychomotor speed tests.[7] The above mentioned studies provide inconclusive results concerning the relationship of OSAS with psychomotor speed which probably has to do with the difference in the amount of severity of the disease in the existing research studies.

Memory and Learning

OSAS patients have repeatedly been presented with serious impairments in memory and learning abilities,[82] such as episodic memory,[84] short-term memory,[69] long-term verbal memory[84] and verbal and visual learning abilities.[86] It has been found that severe OSAS patients' performance was poor in short-term verbal memory tests,[53, 87] long-term learning, and memory tests[53] as well as working,[88] visual and spatial memory tests.[60, 87]

However, not all studies on severe OSAS patients have found memory and learning impairments. In contrast to the above studies that found a serious memory decline in severe OSAS patients, there is a study[8] which showed that severe OSAS patients preserved a good short-term memory, long-term episodic memory, and procedural and working memory and only their performance in immediate recall was found decreased. In line with the above findings, another research study[60] reported no memory decline in severe OSAS patients.

Moderate and severe OSAS patients have been presented with poor verbal immediate, delayed recall and working memory functions.[83, 89] Low scores have been reported on short-term memory and on spatial short-term memory tests in moderate and severe OSAS patients, in contrast to long-term verbal memory ability which was found intact.[79]

However, no significant deficits in episodic memory and working memory have been observed in patients with moderate and severe OSAS.[58] Another study found no differences between normal and mild-to-severe OSAS patients in visual memory and verbal working memory,[81] while immediate and delayed recall of logical memory as well as spatial working memory were found impaired. In addition, patients with moderate OSAS did not show any decline in visual or verbal memory skills.[80] In sum, data with regard to memory functioning in OSAS patients are mixed with future research still remaining to elucidate the relationship between OSAS and memory and learning abilities.

Visuospatial and Motor Constructional Abilities

A small number of studies have reported poor visuospatial and motor constructional abilities in OSAS patients since research in the field was conducted only in the last decade. Patients with severe OSAS have been found to display visuospatial and constructional impairments[60, 85] and moderate and severe OSAS patients in another study have been found to obtain low scores in tests measuring visuospatial and motor constructional skills.[89] This small body of the existing research provides evidence that OSAS has a negative impact on visuospatial and motor constructional abilities; however, the restricted number of studies done in the field delineates the need for further research in this area.

Executive Functions

Executive abilities including mental flexibility, planning, working memory, analysis, synthesis, and organizational skills have been found seriously impaired in OSAS patients.[63, 76, 90] Executive dysfunctions including low performance in phonemic verbal fluency and letter-number sequencing tasks have been observed in patients with severe OSAS.[53, 60, 85, 91] However, there is a study[8] which failed to find a noteworthy decline in executive functions in severe OSAS patients. Regarding moderate and severe OSAS patients, it has been found that they performed poorly in tests that assess executive functions.[67, 83] On the other hand, there are some studies on moderate and severe OSAS patients that did not report any impairment in executive functions.[58, 79] Mild-to-severe OSAS patients have been documented to have significant impairments in mental shift and planning and minimal decline in phonemic fluency.[81]

On the other hand, it has been found that moderate OSAS patients either perform within normal range in executive functioning tests such as the verbal fluency test[68, 80] or that their executive functioning is impaired at a limited amount.[7] It is remarkable that some researchers[92] have found that OSAS patients' performance in some tests measuring executive functions such as the letter verbal fluency[69, 89] were within normal range although their performance was poor in the rest of neuropsychological tests that are sensitive to the detection of executive dysfunctions. One possible explanation is that there is a pattern of both intact and impaired cognitive functions in OSAS patients that make executive impairments difficult to detect.[93] More specifically, it was suggested[88] that there is a specific working memory deficit associated with complex memory tasks and high level memory scanning. Additionally, it has been suggested that deficits in tasks that require high executive functioning are apparent only over the course of the day due to circadian variations or duration of time spent awake.[93] In sum, this review of the literature indicates that the empirical data which examine the relation between OSAS and executive functions are not enough to explain the pattern that executive functions follow in OSAS. Therefore, more research is needed in order to elucidate which are the exact executive functions that are impaired in OSAS and provide an explanation for that.

Language Abilities

Although the bulk of the research conducted on the impact of OSAS on neurocognitive functions focuses on cognitive functions such as attention, memory, and executive functioning rather than on language abilities, there have been some studies on OSAS patients that have shown significant semantic language deficits on their part,[73, 87] although this has not always been the case.[94] The fact that more research has been carried out on cognitive abilities other than language is probably associated with the fact that some of them, for example, attention and memory problems, are more easily noticed by patients themselves as well as by their bed partners and doctors than language deficits are. Research on severe OSAS patients' language abilities[53, 85, 91] has shown that they suffer serious problems in verbal tasks and especially in the semantic domain of language. On the other hand, there is a study[60] which failed to find any significant decline in language abilities concerning the semantic domain, while the same study found a serious impairment in the phonemic domain of language of patients with severe OSAS.

Research on moderate and severe OSAS patients has shown that their performance in semantic tasks was similar to healthy controls.[89] Minimal differences between mild-to-severe OSAS patients and healthy volunteers in semantic and phonemic tasks were also documented.[81] Another study found that moderate OSAS patients' language abilities were within normal range.[80] An interesting finding is that mild and moderate OSAS adolescents have

shown significantly lower scores in semantic and phonemic language tasks.[73]

In sum, the existing research data on language abilities in OSAS patients do not clearly indicate which are the language domains mostly affected by OSAS and to what extent. Therefore, more research is needed in the field taking into account factors other than the severity of symptoms such as the age of the participants because it has been suggested that OSAS occurrence during critical ages of brain growth and development such as childhood and adolescence may cause notable language decline.[73]

Mechanism of Cognitive Impairment in COPD and OSAS Patients

Mechanism of Cognitive Deficits in COPD Patients:

It has been suggested that cognitive impairments in COPD patients are caused by independent factors, such as COPD severity parameters (FEV_1, FEV_1/FVC),[95] oxygen desaturation (SaO_2),[96] oxygen partial pressure (PaO_2), and hypercapnia ($PaCO_2$).[97] More specifically, lung volume impairments defined by FEV_1/FVC (%), FEV_1 (%), and FVC (%) have been presented to correlate with performance in tests, such as the *Mini-Mental State Test*, which examines memory, as well as with orientation, and language skills.[27] **It has also been found[98] that low FEV_1 during middle age was a significant predictor of cognitive disabilities in later life.** Moreover, research has shown that more severe COPD patients presented lower scores in cognitive tests than moderate or healthy adults.[29] In other words, the degree of pulmonary decline plays a crucial role on the level of cognitive impairment.[99] However, the majority of researches failed to demonstrate a significant association between lung parameters (FEV_1, FVC) and cognitive impairments.[39, 46, 96]

Another factor that has been found to be related to impaired cognitive functions is low oxygen desaturation (SaO_2).[22, 100] It has been shown that there is a strong correlation between low baseline oxygen saturation (≤80%) and cognitive impairment.[96] It has also been found that the risk of cognitive impairment increases with decreasing oxygen desaturation.[96] It has been suggested that low nocturnal desaturation or nocturnal blood gas may explain better the cognitive deficits in a similar way in OSAS patients,[46] since hypoxemic COPD patients become more hypoxemic during sleep.[25]

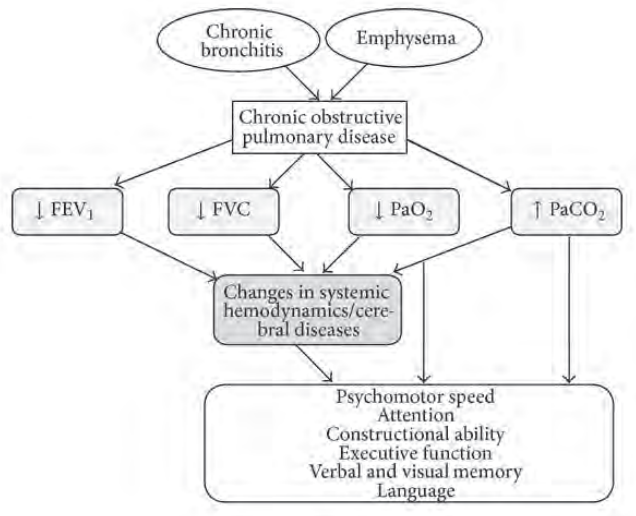
The majority of researches documented a correlation between cognitive functions and the degree of hypoxemia defined by arterial oxygen pressure (PaO_2). More specifically, it has been found that partial pressure of arterial oxygen (PaO_2) is related to complex attention, psychomotor speed, executive functioning, constructional abilities,[44, 47] and visual and verbal short-term memory.[47] The crucial impact of blood oxygen level on cognitive functions can also be proved by the fact that nonhypoxemic patients show less cognitive deterioration.[41] In other words, oxygen-dependent patients have been found to achieve lower scores than controls or nonoxygen dependent COPD patients in cognitive tests[29, 45] which assess verbal memory, delayed recall, and attention.[41] It has also been documented[47] that severely hypoxic patients obtained lower scores than mildly hypoxic patients in simple attention and delayed logical memory tests.

Another important factor that contributes to cognitive decline is hypercapnia or hypercapnea-induced hypoventilation.[43] It has been shown[27] that hypercarbia had a high correlation with information-memory-concentration tests. There are studies that have found a significant correlation between high levels of $PaCO_2$ and deficits in reaction time or logical thinking,[35] in immediate and delayed memory, in complex attention, in information speed processing, in animal-naming of verbal fluency test[47] and in concentration and orientation.[27] Interestingly, it has been shown[47] that neuropsychological test scores were generally more highly correlated with $PaCO_2$ than with PaO_2.

The role of hypoxia and hypercapnia on cognitive decline can also be proved by the fact that therapy, namely, *long-term oxygen therapy* (LTOT) or *lung volume reduction surgery* (LVRS), seems to improve some cognitive functions[101, 102] such as attention and verbal memory[31, 38] or at least partially reverses them.[97] It has also been suggested that the regular use of oxygen has a neuroprotective role in COPD.[96] However, there are studies that have failed to show any association between gas blood and impaired cognitive functions such as attention,[34, 39] language abilities, executive functions,[47] mental speed, and fluid intelligence.[46, 103]

The exact pathophysiological and biological mechanisms that could explain the effects of impaired lungs on the development of cognitive function impairments are still unclear. It has been suggested that low lung functioning may contribute to cognitive disorders by decreasing the oxygen delivery to brain neurons. In other words, low arterial oxygen blood pressure and hypercapnia may develop in these patients as a consequence of their disease and as a result, they contribute significantly to the development of pathophysiology in COPD.[97] It has been suggested that impaired lung functioning causes changes in the central nervous system through processes such as cerebral diseases resulting from impaired fibrinolytic activity, oxidate stress,[99] vascular diseases, and increased proinflammatory cytokines such as TNFR1 that act as a possible systemic mediator via cardiovascular disease between lung functions and brain.[45] Increases in the circulating levels of thrombotic factors may be expected to elevate the risk for cardiovascular disease.[104] In other words, cognitive deficits are mediated by the presence of changes in systemic hemodynamic and cerebral diseases. Moreover, it has been suggested that COPD may accelerate aging processes resulting in decreased cerebral blood flow and oxygen consumption.[49] The potential COPD mechanism by which cognitive functions are affected is summarized in Figure 1.

Figure 1:
Potential COPD Mechanism by Which Cognitive Functions are Affected



Mechanism of Cognitive Deficits in OSAS Patients:

The cause of cognitive deficits in OSAS patients is more complicated than in COPD patients. Some researchers have shown a significant correlation between cognitive impairment and daytime sleepiness related to sleep defragmentation resulting from frequent apneas,[105, 106] while others attribute cognitive decline to nocturnal hypoxemia.[85, 88] Finally, some researchers attribute cognitive impairments to a combination of PSG parameters, namely, AHI, sleep arousals, oxygen desaturation, and sleep architecture.[7, 107]

It has been suggested that cognitive deficits, such as memory impairment and attentional deficits are affected by sleep defragmentation, but impairments in executive functions, in constructional abilities, in motor tasks and in language are caused by hypoxemia.[57, 108, 109] More specifically, several studies found that vigilance impairment derives from changes in sleep architecture[77, 110] that in turn contribute to memory decline.[110, 111] It has also found[88] that sleep architecture (percentage of SWS sleep and REM) is associated negatively with immediate memory and low level memory scanning. In addition, a study[84] showed that the best predictor of episodic memory deficit was the number of microarousals.

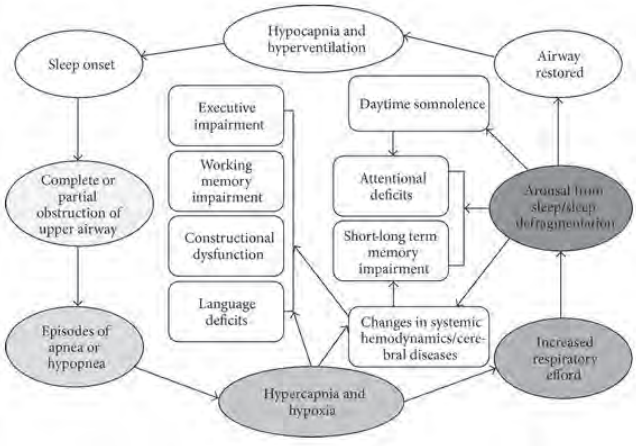
Regarding the effects of hypoxemia on neurocognitive functions, it has been found to be related to psychomotor speed impairments.[98, 112] It was observed[7] that a more severe oxygen desaturation is associated with poorer motor performance and lower processing speed as well as executive dysfunctions.[110] Constructional disabilities have been found to associate with oxygen saturation levels below 80%.[85] A significant correlation was found[60] between the time of oxygen saturation levels below 90% or the lowest peaks of SaO_2 and deficits in phonemic fluency in severe OSAS patients. It has been reported that working memory and high-speed memory scanning deficits, factors pertaining to executive functions, are associated with the degree of hypoxemia (mean SaO_2).[85, 88]

However, the mechanism of cognitive deficits in OSAS is still unclear and the results of the researches are complicated and equivocal. For example, there are studies that link hypoxemia with attention[112] and delayed recall[85] and on the other hand, sleep architecture is related to language and executive functioning.[87] Other researches failed to associate executive functions, such as working

memory, with hypoxemia.[83] It has also been suggested that specific cognitive deficits, such as verbal delayed memory, are associated with both sleep defragmentation and oxygen desaturation.[59, 85] Some studies do not ascribe cognitive dysfunctions to both hypoxemia and sleep deprivation, especially in tasks that assess verbal short-term and long-term memory, nonverbal memory, constructional abilities, language,[8, 79, 89] attention, and executive functions.[8, 78, 93]

As previously mentioned, OSAS patients are presented with significant nocturnal hypoxia, changes in sleep architecture as well as with hypercapnia, and cortical and sympathetic activation.[113, 114] These events cause cardiovascular, cerebrovascular, and metabolic disease as well as sudden death. More specifically, repetitive episodes of deoxygenation and reoxygenation increase the production of proinflammatory cytokines (TNF), C-reactive protein, and chemoreceptors substances that have been associated with the development of atherosclerosis and high arterial pressure.[113, 114] Finally, OSAS patients present blood flow reduction during apneic episodes in left frontal and temporal lobes,[59] in prefrontal and parietal cortex, and in middle cingulated area.[58] In conclusion, the exact biological mechanism that could explain the effects of OSAS on cognitive functions should include hypoxemia, sleep deprivation, and changes in cerebral hemodynamic as well as cerebral diseases. The potential OSAS mechanism by which cognitive functions are affected is summarized in Figure 2.

Figure 2:
The Possible Minimal Mechanism that Causes Cognitive Deficits in OSAS Patients



The Role of Hypoxemia, Hypercapnia and Sleep Defragmentation on Cerebral Cognitive Functions:

As previously shown, COPD and OSAS patients are presented with common neurocognitive deficits**. It has also been noted that hypoxemia is present in both these respiratory disorders and it is associated with the majority of cognitive impairments.** So, we may claim that the cognitive impairments in both diseases are mainly based on hypoxemia and secondary to hypercapnia, changes in systemic hemodynamic, cerebral diseases, and sleep deprivation.

Regarding hypoxemia, it has been found that decreased oxygen transport to brain cells modifies ion channels (potassium, sodium, calcium) and increases glomus cell excitability. In addition, it causes alterations in neurotransmitters (dopamine, acetylcholine, and ATP) and reduces respiration followed by enhancement of sympathetic and respiratory activities which results in changes involving modification in signaling pathways, in neuromodulators (endothelin-1) and their receptors and genome effects.[6, 115] Therefore, brain oxygenation is essential for neural biosynthetic processes situation.[6] It has been found that frequent oxygen desaturation during everyday activity elevates choline level in frontal brain areas that damage myelin and membrane precursors.[45] It is remarkable that even low normal range blood oxygen levels may cause cognitive decline.[6] Moreover, oxygen desaturation may increase hematocrit levels and cause angiogenesis through enhancement of production of vascular growth factors.[6] Finally, it has been claimed that hypoxemia, inflammation, and oxidate stress initiate the process of endothelian dysfunction that plays a significantly role in vascular tone and cellular growth.[116] In relation to the negative impact of hypoxemia on brain regions, it has been found that there is a significant decreased cerebral perfusion in left middle and superior frontal, right superior frontal and left parietal lobes,[41] and in subcortical regions[43] that are related to attention, verbal memory, executive functions, and psychomotor speed.[117] Some regions of the brain, such as the hippocampus, basal ganglia, cerebellum, occipital cortex, and some frontal regions are particularly susceptible to oxygen deprivation than others.[118] Studies on hypobaric hypoxemia also found a neuronal loss

in hippocampus.[119] Furthermore, magnetic resonance image studies revealed a significant gray matter loss and atrophy in several brain regions including cortex, hippocampus, and striatum suggesting that chronic hypoxemia results in neuronal damage and therefore impaired cognitive functions.[120, 121]

Regarding changes in sleep architecture, it is well established that chronic sleep deprivation or sleep fragmentation in healthy subjects may cause a similar decline in alertness, simple attention, psychomotor speed as well as learning, memory, working memory, and executive functions.[122-124] *Functional magnetic resonance imaging* (FMRI) has shown the negative impact of sleep deprivation on specific brain regions, such as temporal to parietal regions and frontal lobe regions. In addition, it has been suggested that long-term sleep deprivation may cause permanent neuronal alterations especially in memory related brain regions, such as the hippocampus[125] as well as reduced activation of frontal and parietal networks and altered functioning within the thalamus.[122] Moreover, it has been found that both short-term and long-term sleep deprivation are associated with the upregulation of hundred of genes in the cerebral cortex and other brain areas. They include genes that are associated with energy metabolism, memory formation, memory consolidation, protein synthesis, and synaptic depression.[126]

As previously seen, hypoxemia and sleep defragmentation cause cellular and molecular changes that lead to disruption of functional homeostasis and altered neuronal and glial viability within particular brain regions,[57, 127] such as frontal lobe[94, 128,129] and temporal cortex.[58] Moreover, hypoxemia and sleep deprivation modulate the expression of inflammatory mediators such as interleukins and tumor necrosis factor alpha.[116]

OSAS and COPD patients may also suffer from hypercapnia. High carbon blood levels increase *cerebral blood flow* (CBF) by 25 to 40%,[130] while at the same time a profound cortical desynchronization occurs that lasts for the duration of the hypercapnic episode and returns to baseline soon after cessation.[131]

However, hypoxia, hypercapnia, sleep defragmentation, or smoking, hemoglobin levels, inflammation parameters, and comorbidities are unlikely to account for all the cognitive dysfunctions.[132] Decline in language abilities and in verbal memory may be associated with age and duration of hypoxemic-hypercapnic chronic respiratory failure.[43] It was found[8] that younger OSAS patients are more sensitive than older OSAS patients to sleep defragmentation and hypoxemia. Another study found that socioeconomic status and adolescent cognitive ability may explain verbal disability, verbal memory decline, or the rate of impairment in memory.[99] In addition, the positive effect of improved quality of life in cognitive dysfunctions was demonstrated.[37] Finally, it has been claimed[133] that intelligence and cognitive functions are interrelated. In other words, high-intelligence may have a protective effect against cognitive decline in OSAS patients, due to increased cognitive reserve. Similarly, a lower IQ correlated significantly with lower scores in neurocognitive tests in COPD patients.[46]

Conclusions

Upon a close review of the literature, it is apparent that since most studies are not homogeneous in COPD and OSAS severity, it is difficult to draw safe conclusions about the reasons of the presence of cognitive impairments in attention, memory, psychomotor speed, and executive functions in those two syndromes. Moreover, the diversity of results is due to differences in methodology and in the types of neuropsychological tests which were used to assess cognitive functions. Furthermore, the treatment duration, low tolerance of treatment, and disease duration are not often taken into account. Few are also known about the etiology of COPD and OSAS, while it is difficult to find out to what extent sleep architecture, blood cerebral flow, gas blood, and comorbidities contribute to cognitive impairment.

In this review, we showed that the effects of sleep fragmentation, hypoxemia, hypercapnia, CBF, and vascocerebral diseases on cognitive functions are intermingled and synergistic. Because of the presence of common cognitive deficits and the significant correlation that these impairments have with low blood oxygen levels in both syndromes, it seems that low blood oxygen pressure is the dominant factor that contributes to common cognitive impairments in both COPD and OSAS.

However, further research is needed which may provide evidence to our claim based on the existing literature and explain the presence of common cognitive impairments in both COPD and OSAS patients.

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Hatherleigh's Note: *Additional typeface treatment was added to text for emphasis. Hatherleigh supplied supplementary title page information, CME quiz, Best Practices, and any medication trade names.*

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L903351

Multiple-Choice Questions

29. Which one of the following is correct regarding *chronic obstructive pulmonary disease* (COPD) and *obstructive sleep apnea syndrome* (OSAS)?

A. COPD is characterized by airflow limitation that is reversible.

B. OSAS is characterized by periodic complete or partial upper airway obstruction during sleep.

C. OSAS is an uncommon chronic respiratory disorder.

D. None of the above is correct.

30. According to the lesson, which one of the following is the major cause of COPD?

A. Alcohol abuse

B. Residing in a dry climate

C. Tobacco smoking

D. All of the above

31. COPD has been found to cause a general cognitive decline in cognitive functions such as:

A. attention.

B. psychomotor speed.

C. memory and learning.

D. All of the above.

32. Risk factors that enhance the probability of OSAS include all of the following, *except*:

A. positive family history.

B. obesity.

C. tobacco and hypnotics use.

D. decreased neck circumference.

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Best Practices in CME

Effects of Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea on Cognitive Functions: Evidence for a Common Nature

By Georgia Andreou, Filippos Vlachos, and Konstantinos Makanikas

ID#: L903351

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

CME Lesson Overview

Patients with *chronic obstructive pulmonary disease* (COPD) and *obstructive sleep apnea syndrome* (OSAS) show similar neurocognitive impairments. Effects are more apparent in severe cases, whereas in moderate and mild cases the effects are equivocal. The primary objective of this review is to present COPD and OSAS's impact on cognitive functions.

Key Point 1: Background on COPD

COPD is a progressive disease characterized by the presence of airflow obstruction secondary to emphysema or chronic bronchitis. In the United States, COPD is the fourth leading cause of death, after heart disease, cancer, and stroke, whereas its prevalence increases with aging. COPD is associated with an increased mortality and morbidity implications such as lung cancer, anemia, pulmonary hypertension, polycythaemia, peripheral oedema, cardiovascular complications, obstructive sleep apnea, chronic infections, and musculoskeletal disorders (e.g., osteopenia and muscle atrophy) as well as nutritional depletion that is caused by increased metabolism during breathiness episodes.

Key Point 2: COPD and Cognitive Decline

COPD has been found to cause a general cognitive decline especially in cognitive functions such as attention, psychomotor speed, memory and learning, visuospatial and constructional abilities, executive functions, and language skills.

Key Point 3: Background on OSAS

OSAS is part of a spectrum of sleep related breathing disorders which also includes *central sleep apnea* (CSA) (apnea without respiratory effort), mixed sleep apnea (episodes of obstructive sleep apnea and central sleep apnea), upper airway resistance syndrome (increased respiratory effort without apnea or hypopnea), and snoring.

Key Point 4: OSAS and Cognitive Decline

It has been repeatedly documented that OSAS has a negative impact on a wide range of cognitive functions. Attention, memory, psychomotor speed, visuospatial abilities, constructional abilities, executive functions and language abilities are among the most impaired cognitive domains in OSAS patients.

Key Point 5: Discussion

The effects of sleep fragmentation, hypoxemia, hypercapnia, CBF, and vascocerebral diseases on cognitive functions are intermingled and synergistic. Because of the presence of common cognitive deficits and the significant correlation that these impairments have with low blood oxygen levels in both syndromes, it seems that low blood oxygen pressure is the dominant factor that contributes to common cognitive impairments in both COPD and OSAS. More research is needed to support the evidence of this claim.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Narcissism in DSM-5 Section III Model for Diagnosis of Personality Disorder

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

KEYWORDS: Narcissism • Narcissistic Personality Disorder • Empathy • Self-esteem • Emotion Regulation • Suicide

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) use the DSM-5 Section III hybrid dimensional and trait-focused diagnosis for narcissistic personality disorder; (2) apply a collaborative, exploratory diagnostic strategy that identifies the range of narcissistic personality functioning, fluctuating self-esteem, and the co-occurrence of both self-enhancing grandiosity and self-depleting vulnerability; and (3) understand the influence of comorbid conditions, suicidality, bipolar disorder, and substance use disorder on the diagnosis of NPD.

LESSON ABSTRACT: Identifying patients with narcissistic personality disorder, or NPD, has been challenging, foremost because the NPD diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) has not covered relevant aspects of narcissistic pathology. Consequently, discrepancies between the patients' experiences and clinicians' observations have made it difficult to reach a meaningful diagnosis that is in agreement with the patients' experience and is informative for continuing treatment. This lesson will inform readers about the new diagnostic criteria for NPD in the DSM-5 Section III, which applies a combined dimensional and trait model for personality disorders, including level of self and interpersonal functioning and pathological personality traits. The evaluation of regulatory patterns and impairments in sense of identity, self-direction, empathic capability, and intimate interpersonal relationships and traits of grandiosity and attention seeking are applied to two case vignettes. The influence of psychiatric conditions often co-occurring with NPD—suicidality, bipolar disorder, and substance use—on narcissistic personality functioning and the process of diagnosing NPD will be discussed. The integration of the diagnosis with alliance building and preparation for treatment requires an exploratory collaborative strategy that aims to help the patient attend to the range of his or her personality patterns and internal experiences.

COMPETENCY AREAS: This lesson will increase awareness of the new hybrid combined trait and dimensional model of personality disorders, as outlined in DSM-5 Section III, and cover the major improvements in identifying narcissistic personality disorder through the integration of functional range and fluctuations, indications of narcissistic self- and emotion regulation, and accompanying interpersonal patterns.

Introduction

The trait-based criteria established for *narcissistic personality disorder* (NPD) introduced in the *Diagnostic Statistical Manual for Mental Disorders*, DSM-III in 1980,[1] has increasingly been criticized for its failure to attend to the full range of narcissistic personality pathology and identify patients whom clinicians consider to have an NPD diagnosis.[2-6] Despite some changes in the recent editions of the DSM, significant traits of pathological narcissism remain omitted (i.e., shame, fragility, perfectionism, and self-criticism). People with narcissistic pathology who do not meet any combination of the five required criteria will not be correctly diagnosed, and the focus on external characteristics tends to dismiss the importance of fragility, internal distress, and painful experiences of self-esteem fluctuations and emotional dysregulation. Further, the range of functioning in people with pathological narcissism and NPD, from high, competent, and consistent capability to inconsistent, fluctuating, or low functioning with comorbid mental illness, is not taken into consideration. Consequently, clinicians' definition and usage of the NPD diagnosis have differed from the official set of DSM criteria, and patients tend to oppose being "labeled" as NPD, conceiving it as prejudicial or incongruent with their own experiences of their problems.[7]

The inclusion of NPD in the DSM-5[8] Section III alternative hybrid model, which identifies both dimensional aspects and traits of pathological narcissism, is a major step forward.[9,10] The DSM-5 Section III combines an integrative diagnostic formulation of pathological narcissism and NPD that focuses more on the regulatory range of narcissistic personality functioning and less on overtly symptomatic- or phenotypic-based features. This diagnostic model, a proposal awaiting further studies, identifies specific difficulties and moderate or greater impairments in personality functioning—that is, identity and self-direction related to self and empathy and intimacy in interpersonal relations. The typical features of NPD are variable and vulnerable self-esteem, with attempts at regulation through attention- and approval-seeking, and either overt or covert grandiosity.[8 (p767)] This encourages a diagnostic process that attends to both the externally noticeable aspects of narcissistic functioning as well as those internally hidden and/or primarily identified by the patient him or herself. It also invites a collaborative, exploratory diagnostic process, which differs from a predominantly clinician-based diagnosis, which is more based on the externally notable and provocative narcissistic traits.[10] The patient has to be engaged and feel that the diagnostic process and formulation make sense and correspond to his or her subjective experiences. The challenge of bridging the gap between externally observed narcissistic features and the patients' subjective perspectives and experiences of their problems may call for a gradual and ongoing diagnostic process as part of alliance building. The aim of this lesson is to outline a collaborative diagnostic process anchored in a dimensional approach to narcissistic personality functioning, which can be meaningful and informative to the patient and prepare and motivate them for continuing treatment.

Clinical Case Example #1

Mrs. Adams, a 42-year-old married woman, came for a consultation after facing a major crisis in her marriage and an ultimatum at her work place. Initially, she was self-assertive and condescending, stating that she never thought she would have to seek psychiatric help. Gradually, however, she became noticeably upset, angry, and confused as she described an escalating development over the past months that had culminated in a situation she found to be both unfair and retaliatory, but also potentially threatening. Her husband had told her she was narcissistic—self-centered, unempathetic, disinterested in her family, and focused only on her work and career. He had even threatened to move with their daughter closer to his family in another part of the country. Her supervisor had stated that she was uncooperative and interacting with her subordinates in a very authoritative, critical, and demeaning way. If she did not change, she would be asked to leave the company. Mrs. Adams was a researcher and project manager in a large corporation and had over the years enjoyed success and contributed to significant financial and scientific advances. She married and gave birth to a daughter who is now

6 years old. Her husband had been working from home and been the primary caretaker of their child. Mrs. Adams had noticed that she recently had increased her daily alcohol consumption to help calm down and improve her interpersonal functioning. She also tended to wake up in the middle of the night with anxiety, and, for the first time in her life, she had begun thinking about suicide. She had no prior psychiatric history and had never been in treatment. She did report driving herself excessively hard and periodically spending up to 14–16 hours/day at work. She also reported severe anger outbursts, which she had been able to control so they had not jeopardized her overall functioning.

The clinician faced an immediate discrepancy in Mrs. Adams' presentation between her articulated and provocative forcefulness and critical, blaming attitude towards others, in addition to her confusion when anticipating being left without family and work. He asked Mrs. A about her understanding of her husband's and supervisor's perceptions of and reactions towards her, and she immediately dismissed them as unfair and retaliating, rooted in their envy of her success; nor had she noted her co-workers dissatisfaction or reactions towards her. She had high standards and demands to be able to excel in her company, and she expected others to measure up. She also wanted her present project to get worldwide recognition, and her primary concern was the progress of her projects. She did not see that she was inattentive or unconcerned towards her child and husband, but admitted that over the years she had found it increasingly difficult and confusing to identify herself as a mother to a growing and gradually more attention-seeking and demanding daughter. This contrasted with her high esteem as a successful professional. She referred to her father, who was a professor, and observed that her mother had spent most of her life taking care of the children (Mrs. A and her 4 siblings). Mrs. A admitted feeling very disdainful towards her mother, whom she saw as inferior and unable to make something out of her life. When asked how she perceived her problems, Mrs. A began to shake, saying that she was afraid of losing direction and control, but foremost she was afraid of losing her important affiliations—she believed that she loved her husband, but she felt distant from him and tended to get angry and frustrated with him. She realized that she found it increasingly difficult to simultaneously be a wife, a mother, and a successful professional woman, and she admitted that her work was her lifeline and pride.

Clinical Case Example #2

Mr. Brown, a 33-year-old single man, was referred to a residential treatment program after a serious suicide attempt. This was precipitated by him feeling increasingly empty, disillusioned, and pessimistic. The woman he adored and had considered to be a good fit for his envisioned future had suddenly announced that she did not want to pursue a relationship with him. Her departure evoked intense reactions of devastation and overwhelming feelings of worthlessness, loneliness, as well as a loss of hope and sense of future. For a long time, however, he had felt detached and confused, both vocationally and socially. Mr. Brown was very intelligent and talented in many areas, such as music, computers, wrestling, and chess, and he had won competitions and received awards in each of these areas, but he had never been able to sustain a living and build on any of his significant talents. To the contrary, except for brief periods, he had been out of work and was financially supported by his father for most of his adult life. He described to the intake clinician that shame and inferiority had begun to "haunt" him, and that he had significantly increased his substance use (alcohol, marijuana, and cocaine). Mr. Brown came across as stoic, confident, and detached, convinced that under the right circumstances he would be able to be very successful. Initially he blamed his parents, foremost his father, for never believing in him or supporting him to succeed. When asked to further describe what

happened in times of success, Mr. Brown said that it was as if he could not believe in himself, as if he lost control of his abilities, got confused, and lost sense of who he was. He found it very aggravating. He could focus and work hard to reach a point of success, but once he was recognized and received the award or acknowledgement, it was as if it disappeared. He used to blame others or circumstances, but he had gradually come to a realization that it was something happening within himself that he did not understand. Similarly, in his relationships, he had often engaged with people who he felt stimulated and supported his achievements and creativity but tended to reach a point where he either anticipated or directly experienced them losing interest in him. The sequence remained unclear—that is, whether Mr. Brown himself lost confidence and detached or whether he anticipated or perceived others losing confidence in and detaching from him. Growing up, Mr. Brown described himself as a perceptive and very sensitive and reactive child. He found his mother to be demanding and intolerant, whereas his father could be inviting and supportive, but then suddenly change and become overpowering, critical, and angry. He felt he was constantly on guard, relying on his attention and observations to protect himself and oscillating between a sense of measuring up and failing, never able to assure himself about the outcome or more consistent, competent functioning.

Applying a Dimensional Diagnostic Approach to NPD

Several aspects of narcissistic personality functioning and its co-occurrence with other mental conditions are best conceptualized in terms of a dimensional range. **First, narcissism ranges from healthy and proactive to pathological and malignant.** Aspects of normal, healthy narcissism can co-occur with even severely pathological narcissism and NPD.[11] **Second, the range from overtly striking and provocative to covertly hidden and unnoticeable narcissistic patterns and features is typical for people with NPD.**[12] Protective regulatory patterns, such as a need for control and avoidance, along with shame, denial, or limited self-disclosure, can easily lead to diagnostic misinterpretations and bypassing of narcissistic features and personality functioning. On the other hand, extremely extravert dominance with bluntly provocative controlling, manipulative, or competitive personality patterns can also lead to disregard of underlying fragility and insecurity. Third, narcissism can be influenced by life context and specific events that can either enhance the severity of or have a corrective impact on pathological narcissistic patterns.[13] **Fourth, although one can be more phenotypically prevailing, vulnerability with insecurity and inferiority co-occur with self-enhancing grandiosity, arrogance, and aggressivity in people with pathological narcissism and NPD.**[2,14,15]

In sum, patients with NPD can be consistently high functioning, vocationally successful, and/or socially adjusted and connected. They may develop relationships and life contexts that support their sense of agency and capability and concurrently protect their underlying vulnerability. Changes in life experiences or actual circumstances may lead to a sudden unfolding of such fragility with gradual impairment in personality functioning and aggravation of pathological narcissistic patterns and features. However, patients with NPD can also present with fluctuating personality functioning, ranging from self-enhancement and assertiveness to inferiority and insecurity, and with more or less severely disabling narcissistic character patterns and long-term impairments. Such functional fluctuations can be dependent on interpersonal as well as social, vocational, or general life contexts. Some suffer from narcissistic trauma;[16] others have malignant, psychopathic, or antisocial traits;[17, 18] and still others can have comorbid mental disorders (mood disorder, substance use disorder, PTSD).[19, 20] Patients' phenotypic presentation can also vary. Some are charming and friendly, and others are competent and assertive; some are shy and timid, and others are intrusive and controlling; some are domineering and competitive, and others are aggressive and manipulative.[3, 10, 21]

Attention to the dimensional self-regulatory nature of pathological narcissism with a focus on diagnostically meaningful characteristics can help to identify the patient's fluctuating self-esteem and the co-occurrence of both self-enhancing grandiosity and self-depleting

vulnerability. Such a diagnostic approach can also help differentiate temporary fluctuating or externally evoked features and patterns from enduring indications of pathological narcissism—and especially help to recognize narcissistic individuals' internal suffering related to insecurity, self-criticism, anxiety, shame, and fear.

Self-regulatory Dimensions

Identity:

Sense of identity relates to self-awareness: and the ability to self-assess, identify, and maintain roles and consistently regulate self-esteem. In addition, the ability to experience, tolerate, and regulate emotions also affects the identity. A prime indication of NPD is the patients' difficulty in maintaining a stable sense of self-regulation and self-esteem and presenting with more or less extreme fluctuations, ranging between enhanced or significantly exaggerated self-evaluation and deflated self-depreciation or inferiority. The patients' sense of self and identity is strongly influenced by their perceptions of external confirmation and support, which can be either primarily interpersonal or more objective (e.g., evidence of competence, acknowledgements, or social or financial status). Sense of self, identity, and emotion regulation are all affected by self-appraisal and the resulting level of self-esteem. Consequently, strong feelings of shame, inferiority, rage, or worthlessness can accompany low self-esteem, and excitement, superiority, overconfidence, and arrogance can indicate enhanced self-esteem. In the case examples above, Mrs. Adams described how her identity and competence as a professional woman defined her self-esteem. Facing her role as a mother, however, tended to challenge and undermine her confidence. She also described intense emotional reactions when her self-esteem was threatened or lowered. Mr. Brown noticed the sudden shifts in his sense of self-esteem and competence when facing evidence of his achievements. Paradoxically, for some patients with NPD, such external evidence can be both desirable and at the same time extremely challenging—that is, evoking self-criticism, doubt, fear of exposure, retraumatization, or a deep sense of not deserving. In addition, the loss of his female partner also caused intense reactions of both loss of self-esteem and a sense of male worthlessness.

Self-direction:

Aspirations and goals based on a realistic assessment of one's own capabilities are central for self-direction. Appropriate behavioral standards, the ability to feel fulfillment in different areas of life, and self-reflective capability are additional general indicators. Self-direction relates to self-agency, a sense of authorship and awareness of the effects of one's own actions, a realization that one can be seen and valued, the ability to evoke others' responses, create meaning, and make things happen.[22, 23] Self-agency and sense of internal and/or external control are considered central for narcissistic self- and self-esteem regulation,[24] and loss thereof can drastically escalate pathological narcissistic functioning. In the DSM-5 Section III, NPD is characterized by instability and incoherence in goal setting and by being overly focused on gaining external approval or evidence of accomplishments. Similarly, personal standards can be high and influenced by perfectionism and high aspirations or by efforts to gain attention or admiration. They can also be too low and based in a sense of entitlement and a sense that others should provide and facilitate the necessary conditions. Higher functioning people with NPD can be extremely goal-directed and have particularly high standards that may limit their ability and sources for fulfillment in life. Their reflective ability can be influenced by overly intellectual or otherwise specified self-definitions. More impaired patients with NPD, on the other hand, can have a more or less compromised ability to sustain their goals and understand their internal experiences. In addition, they are often unaware of their own motivations.

Mrs. Adams conveyed a long-term ability for direction, agency, and attainable goal setting in her professional career that was anchored in relatively realistic standards and evaluations of her developing capabilities. However, as she expanded her life context by getting married and becoming a mother to her child, compromises in her self-direction and limitations in her sense of agency became more apparent. She was facing incompatible goals and reacted by becoming excessively focused on her professional accomplishments, unable to reflect upon and attend to her role as a wife and her experiences and challenges as a mother. Mr. Brown, on the other hand, had several areas of competence that he could access, expand on, and enjoy temporarily—under

certain favorable conditions—but he lacked anchored goals beyond a certain level of temporary achievements. His personal standards were inconsistent or generally unclear and low, and he lacked a sense of authenticity to be able to convert temporary achievements into long-term goals and sustaining capabilities.

Empathy:

The ability to recognize others' perspectives and identify and understand others' experiences is an essential part of empathic capability. In addition, awareness of one's own effects on others and openness to modulate accordingly represent an essential interpersonal aspect of empathy. Lack of empathy has long been considered one of the most acknowledged and striking traits of NPD. However, recent neuroscientific and neuropsychological research has radically changed the conceptualization of empathy, from an asset that is either present or absent to a multifaceted capability and a process that is affected by both external circumstances and internal factors. More specifically, research has identified several features in empathic functioning and processing in people with NPD, including relatively intact cognitive empathic functioning but impairment in emotional empathic ability, which is affected by emotion dysregulation (impaired emotion recognition, accuracy, and tolerance) and a tendency to focus on self when facing and processing others' emotions. They also tend to have motivational- and self-regulatory-based fluctuations with interpersonal engagement and disengagement in their cognitive empathic functioning, and they tend to overestimate their own emotional empathic capability.[25-30] **In other words, people with NPD have the ability to cognitively identify the feelings, thoughts, and intentions of others, but their ability to respond to others' emotional states is compromised.** Their empathic capability is also affected by fluctuations in their self-esteem. The dimensional diagnostic model in the DSM-5 Section III specifies empathic capability in NPD as a general impairment in the ability to recognize and identify with the feelings and needs of others, with a tendency to be excessively attuned to others' reactions if they are relevant to the individual him or herself, as well as with over- or underestimations of their own effects on others.

Mrs. Adams tended to dismiss or respond negatively to others' reactions towards her. She experienced difficulties as a mother attending to and engaging with her daughter. The incompatibility between her identity as a professional and a mother obviously caused fluctuations in her self-esteem, which further compromised her empathic ability. Her unawareness of how she could affect others' feelings and experiences was also striking. The focus on her own accomplishments, meeting of standards, and demands also tended to redirect her focus away from others and onto herself. Mr. Brown, on the other hand, could, after his recent crises, show some more interest in and willingness to attend to his impact on others. He noticed that, under certain circumstances, he could be attentive and emotionally engaged, especially towards his girlfriends, when he felt that their relationships were going well and that they could have a future together, or with temporary partners in projects when he sensed that together they were aiming towards the same goals, or when he managed to reach a level of success.

Intimacy:

Affected by their compromised empathic functioning, people with NPD tend to experience considerable problems in their close relationships. Patterns of dismissive attachment or patterns that involves several attachment states, including angry or overwhelmed preoccupation, tend to characterize intimate relationships.[31] Some tend to detach both socially and intimately while others are able to maintain more functional or distant relationships—for example, being consistent collaborators, reliable providers, or even supportive parents during certain developmental stages in their children's lives that do not interfere with their self-esteem. Still others struggle with challenging interpersonal efforts to preserve control and self-esteem, to tolerate differences and disagreements, and to balance anxiety, anger, and boredom. Section III in the DSM-5 identifies relationships in people with NPD as superficial and, foremost, as serving self-esteem regulation. Their ability for mutuality is constrained by little genuine interest in others' experiences, and their engagements are primarily driven by a need for personal gain. Mrs. Adams had been a reliable provider for her family but was increasingly unable to relate to her husband and daughter in a genuine and intimate, caring way. She preferred more functional collaborative relationships with subordinates, who could contribute to enabling her accomplishments, and with whom she felt more in

control. Mr. Brown struggled with self-esteem fluctuations that were influenced by his perception of others' attention to and support of him. His own patterns of approaching vs. distancing, and engagement vs. disengagement, were both related to building achievements and gaining admiration. Under certain circumstances, he could be intimate when he felt that a partner matched or shared his visions of the future.

Personality Traits

Grandiosity:

Grandiosity remains the central diagnostic trait for NPD and the most significant marker of enhanced self-esteem regulation. It is expressed foremost in the patient's beliefs and experiences of him or herself being enhanced—that is, important, privileged, special, unique, superior, limitless, or self-sufficient—and is usually accompanied by high aspirations, ideals, fantasies, or entitlement. The degree of reality versus imagination or illusion in such grandiose self-perceptions is an important indicator of the severity of narcissistic psychopathology. In other words, the individual's ability to function with actual skills, agency, competence, and personal assets, especially during times of challenging functional or self-esteem fluctuations, is an important indicator of the degree and function of grandiosity. Inferiority, insecurity, fragility, and hypersensitivity co-occur with grandiosity, and fluctuations in between can be noticeable in interpersonal self-enhancing, self-serving, controlling, condescending, or aggressive interpersonal attitudes or behaviors. Grandiosity is also affected by the presence of depressivity[32] and by mood disorders, substance use, and bipolar spectrum disorder. In these cases, grandiosity may be hidden in fantasies or compromised by disillusions that contribute to co-occurring psychiatric conditions.

Mrs. Adams' sense of grandiosity had been closely connected to her professional success and foremost expressed in extremely high aspirations and a sense of limitlessness. In phases of progressive accomplishments, indications of narcissistic grandiosity were less noticeable and impairing, but with escalating demands in her increasingly diverging and demanding life context, her vulnerability, fear of failing, and interpersonal difficulties unfolded, and more striking indications of grandiose entitlement with high aspirations and ideals beyond the achievable became more apparent—in addition to self-centeredness and condescending and aggressive interpersonal behavior. Mr. Brown's grandiosity was primarily anchored in his visions and fantasies about his capability and future and spurred by brief experiences of agency, success, and agreeable relationships. However, underlying vulnerability, vague and inconsistent self and goal directions, and an inability to sustain agency and competence can lead to extreme self-esteem fluctuations with grandiose beliefs and aspirations, self-centeredness, and social or interpersonal distancing.

Attention Seeking:

Admiring attention, combined with approval seeking, has long been considered a significant trait of NPD. Some people with NPD can be strikingly charming, domineering, competitive, or extravagant as a way to gain attention. Others achieve their attention by being articulate, perfectionist, accomplished, or creative, and still others can engage in deceptive or dishonest activities to attract temporary attentive admiration. The degree of underlying reality-anchored base (i.e., actual capability and achievements, creativity, beauty, etc.) for gaining attention and admiration can vary and indicates the individual's level of functioning. From a self-regulatory perspective, underlying the excessive need for attention and admiration are the individual's self-criticism, self-undermining of genuine appreciation, and fear of pursuing actual and overt indications of competence, foremost due to fear of exposure, criticism, or failure.[33]

Mrs. Adams had gained reality-anchored and well-deserved attention and admiration through her professional competence and success, but gradually this professionally anchored attention began to take on a function of counterbalancing her basic sense of insufficiency and insecurity in her private life as a wife and mother. It became more obvious that she experienced her husband's and daughter's needs for her attention as demanding and overwhelming. Mr. Brown, on the other hand, strongly desired attention and admiration, but he could not maintain relationships and competence—the prime sources of attention from others. Inability to take ownership of his capabilities, and fear of exposure and not receiving real and sustaining admiring validation for his accomplishments, led him to engage in procrastination,

avoidance, and blame. In addition, he also struggled with a strong conviction that attention and admiration from others were temporary and thus non-enduring.

Influence of Major Psychiatric Conditions on the Diagnosis of NPD

Suicide in NPD Patients:

Suicidal behaviors in NPD patients, though relatively common, are still empirically under-researched. Figures regarding prevalence are lacking, and the literature on risk factors is based on very few, yet to be replicated studies (Table 1). Formulating suicidal risk in terms of the dynamics of pathological narcissism is critical for understanding these behaviors in patients with NPD. **Some suicidal behaviors appear in the absence of major psychopathology or mental illness.[43] In these cases, the dynamics associated with NPD directly contribute to suicidal risk.**

The presence of comorbid disorders increases the risk of suicide.[70] **In these cases, suicide stems from dynamics associated with the comorbid conditions (e.g., hopelessness in MDD, legal issues in *antisocial personality disorder* [ASPD]) or effects of NPD (e.g., humiliation due to functional impairment stemming from MDD; a sense of humiliation, defeat, and entrapment in cases of legal or vocational problems in ASPD, and humiliation due to impulsivity and interpersonal or emotional instability stemming from comorbid BPD).** In all these cases, NPD strongly affects and colors the suicidal dynamics.

Some specific narcissistic personality traits also contribute to suicide risk. Unrealistic, rigid standards that fuel self-shaming, self-critical, and self-punitive thinking increase the risk for suicide. Unrealistic expectations from others can lead to decompensation following interpersonal disappointments. Difficulties with self-disclosure stemming from a lack of self-awareness, dissociation, or shame can contribute to the risk for suicide, which comes as a surprise to others. Some NPD patients plan their suicide in very deliberate ways and take pride in its planning and execution. **Thus, studies show an increased suicide risk in less impulsive patients. Dissociation in the form of detachment from self and one's body, derealization, depersonalization, and a chronic and deadening sense of numbness contribute to despair and a desire to escape through suicide.** Body hatred expresses an inner struggle within conflicted self-representation, and it leads to suicide through the desire to discard an imperfect or hated body. Other NPD patients are plagued by paralyzing confusion around their sense of self. They feel confused and pulled in different, often contradictory, directions, leading to chaos and conflict in their lives. Suicide might follow as a way to abolish the confusion. Chronic, characterological anger, irritability, and rage predispose to suicidal behaviors. In these cases, suicidality is in service of calculated spiteful attacks on others, sometimes even the therapist. In other cases, suicide is a self-destructive expression of uncontainable rage.[71, 72]

Table 1:
Risk Factors for Suicidal Behaviors in NPD Patients

Findings	Psychiatric Conditions	Personality Traits	Life Events	Emotional States
	Major affective disorders Substance use disorders Panic disorder Anorexia nervosa Antisocial personality disorder Borderline personality disorder	Perfectionism Lack of self-disclosure Low impulsivity Dissociation Body hatred Inconsistent self-representation Chronic anger	Legal and disciplinary problems Unemployment Physical illness Financial problems Problems at school or job Aging	Despair Anger Entrapment Humiliation Defeat
Empirical support	References: 34-42	References: 43-62	References: 63-66	References: 66-69

Life events usually interact with narcissistic vulnerability and personality traits and propel the patient into an acute suicidal crisis.[73] Many of these life events are self-generated,[74] thus adding to a sense of humiliation, regret, and entrapment to the mounting desperation. Suicidal crises in NPD patients can stem from a whirlpool of intolerable negative effects, especially desperation. Some feeling states are especially pernicious: entrapment, defeat, and humiliation. These intense affective states are "common pathways" through which other risk factors lead to suicidal behaviors.

Bipolar Disorder and NPD:

Differential diagnosis between these two conditions is complicated by overlaps in the following characteristics: grandiose sense of self, impulsivity, and irritability. The differential diagnoses require the clinician to take an in-depth, exploratory, and longitudinal perspective since, in many cases, the long-term course of the disorder is especially informative.

Grandiose sense of self in bipolar disorder patients is related to alterations of the mood and mostly independent of life-events, whereas in patients with a primary NPD diagnosis, the grandiose sense of self is more persistent and somewhat reactive to life events related to success and failure. Impulsivity in bipolar patients is related to disregard for consequences and a sense of invincibility, whereas in NPD patients, impulsivity is a desperate defense against shame, humiliation, anger, and boredom. Anger and irritability in bipolar patients are mostly connected to mood fluctuations and are primarily biologically determined. In NPD patients, anger is precipitated by real or perceived threats to self-esteem.[75]

During bipolar episodes, the presence of NPD criteria, such as the need for the admiration and envy of others, typically signals the presence of NPD.[76] In addition, NPD patients, but not bipolar disorder patients, present difficulty in assessing self and others in a deep way, suggesting an unintegrated sense of self and others.[77]

The importance of a longitudinal perspective in clarifying the diagnosis has been highlighted by the finding that during manic and hypomanic episodes, most bipolar patients exhibited most NPD criteria, whereas only 11% of euthymic bipolar patients met the criteria for NPD.[76] **In other cases, NPD and bipolar disorder are comorbid.** The investigation of comorbidity is complicated by the difficulty of ascertaining one condition in the presence of the other. Studies report that bipolar disorders are present in 5%-11% of NPD patients, and about 0%–11% of euthymic bipolar patients meet the criteria for NPD.[20, 76, 78]

Ruling out bipolar disorders vs. ascertaining comorbidity has prognostic and treatment implications. Bipolar disorder confers a less favorable course and highlights the importance of a dual focus on medication and skills training for the management of bipolar disorder as well as psychotherapy for NPD. The absence of bipolar disorder prioritizes psychotherapy and the patient's role as the most important vehicle of change.

Substance Use Disorders and NPD:

Between 24% and 64% of NPD patients meet the criteria for any *substance use disorder* (SUD), making SUD the third most prevalent comorbidity in NPD.[19, 78] NPD is present in 6% to 7% of patients with alcohol use disorder and in 13% to 38% of patients with other SUDs.[78] The constant, insatiable need for self-enhancement and the pervasive need to sustain an unrealistic, grandiose self-image fuel the vulnerability to use substances. Substances such as alcohol, benzodiazepines, opiates, and cannabis decrease disillusionment with self. These substances are typically used to relieve stress and anxiety in ambitious and career-driven patients. Medical residents and physicians are some of the victims of this vulnerability.[79, 80]

Cocaine and other stimulants create an illusion of superiority, grandiosity, and efficacy. These substances have a special appeal for NPD patients: They support grandiose self-perception and the illusion of superiority while lacking the same life-threatening withdrawal as alcohol or benzodiazepines, thus minimizing the risk of much-feared dependence, which is especially threatening for NPD patients. Cocaine is also capable of creating a valued sense of efficacy, making it especially challenging to give it up.

No treatment that targets NPD is effective in the presence of active substance use, urging the clinician to help the patient stop substance use if a successful treatment is being considered. Similarly, NPD predicts the persistence of substance use,[81] suggesting that addressing

NPD is critical in combating SUD, and that it is not likely to improve as a result of treatment for SUD alone. In these comorbid cases, a dual, concurrent focus on SUD and NPD is critical.

The Diagnostic Process and Alliance Building

Patients with NPD require a goal-oriented, pragmatic approach that includes the evaluation of both their strengths and vulnerabilities and focuses on building a collaborative alliance. The diagnostic evaluation tends to activate the patients' self-protection and control. Some patients can be effectively defensive, focusing on details or seemingly relevant issues while avoiding more urgent or deeper and challenging problems. Others can mobilize plasticity and adjustment, following along and agreeing with the clinician's comments without revealing or changing their own opinions.[82] Still others may readily become argumentative, aggressive, and critical. The patient's reason and motivation for seeking treatment and engaging in a diagnostic process may not relate to or engage their own experiences of problems.[83] Similarly, the clinician's observations of the narcissistic patients' functioning may not concur with the patients' own experiences of themselves or formulations of their problems. Focusing on the exploration of a recent event that can highlight and inform about fluctuations in self-esteem and agency can be a useful start.

When the diagnostic assessment is part of initiating an individual treatment, special attention should be dedicated to identifying various treatment-interfering behaviors as they unfold in the diagnostic process. It is important to work collaboratively with the patient and establish reasons why these behaviors pose a threat to the effective use of therapy and what can be done to address them. This stage, referred to as a contracting stage,[84, 85] is critical in slowing the patient down and containing current and future acting out that threatens the effectiveness and, at times, the very existence of therapy.

Connecting the diagnostic assessment with the identification of realistic and measureable goals that the patient is willing to pursue is yet another collaborative effort. Many patients with NPD tend to resist such an endeavor due to fears of commitment and failure or a reluctance to give up narcissistically regulatory or gratifying patterns. Finally, both patient and therapist need to come to a clear agreement regarding their respective roles and responsibilities, including what to expect from therapy and what can be done when in crisis. Continuing collaborative exploration of emotional and interpersonal experiences can serve to integrate the diagnostic process with the alliance building towards a deepening of the therapeutic process, with the goal of helping the patient to become more curious about and attuned to inner experiences and to shift away from pathological certainty, self-loathing, aggrandizing, or admiration seeking.

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Multiple-Choice Questions

33. Narcissism ranges from:

A. healthy and proactive to pathological and malignant.

B. self-enhancing and assertive to inferiority and insecurity.

C. overtly striking and provocative to covertly hidden and unnoticeable features.

D. All the above

34. Individuals with *Narcissistic Personality Disorder* (NPD):

A. have the ability to cognitively identify the feelings, thoughts, and intentions of others.

B. are isolated and cannot engage in relationships with others.

C. are not high functioning or vocationally successful.

D. None of the above

35. Bipolar disorder in NPD patients is:

A. always a better diagnosis than NPD to give to the patient.

B. is very clear in its differential diagnosis.

C. possible in some NPD patients, as a comorbid condition.

D. not treatable.

36. All the following statements about suicide in NPD patients are true, *except*:

A. NPD is typically not impulsive.

B. NPD is always related to a major comorbid Axis I disorder.

C. NPD is triggered by intense humiliation.

D. NPD is happening in the context of self-esteem-relevant life events.

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Best Practices in CME

Narcissism in DSM-5 Section III Model for Diagnosis of Personality Disorder

By Elsa Ronningstam, PhD; and Igor Weinberg, PhD

ID#: L003352

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 enables clinicians to integrate a combined dimensional and trait-focused diagnostic approach to the diagnosis of *narcissistic personality disorder* (NPD) that focuses on the range of patients' strengths and vulnerabilities in self- and interpersonal functioning.

Key point 1: Fluctuations in Narcissistic Personality Functioning

Fluctuating narcissistic personality functioning can range from self-enhancement and assertiveness to inferiority and insecurity and depend on interpersonal, as well as social, vocational, or general life contexts.

Key Point 2: Compromised but not a Lack of Empathic Capability

Individuals with NPD have a relatively intact cognitive empathic functioning, but emotional empathic ability is impaired or fluctuating, foremost due to emotion dysregulation (impaired emotion recognition, accuracy, and tolerance), self-centeredness, and motivational- and self-regulatory-based fluctuations in interpersonal interactions.

Key Point 3: Suicidality in NPD

Suicidality in NPD patients is typically a non-impulsive attempt to manage fragile self-esteem and grandiosity.

Key Point 4: Comorbid Substance Use and NPD

Substance use disorders in NPD patients require separate clinical attention and should in most cases be conceptualized and assessed in the context of self-esteem regulation.

Key Point 5: Differentiating NPD from Bipolar Disorder

There can be overlaps between NPD and bipolar disorder in the features of grandiose sense of self, impulsivity, and irritability, which requires an in-depth exploratory evaluation, especially of the long-term course of the disorder.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Internet Addiction: Comorbidity with Psychiatric Disorders

Aviv Weinstein, PhD

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

KEY WORDS: Internet Addiction • Problematic Internet Use • Comorbidity • Anxiety • Depression

LEARNING OBJECTIVES: Clinicians will review recent evidence on the assessment, diagnosis, and comorbidity of Internet addiction. They will interpret studies and diagnostic information including comorbidity with other psychiatric disorders. Readers will review the evidence on the relationship between Internet addiction and comorbid psychiatric disorders and the development of these disorders.

LESSON ABSTRACT: Internet addiction or *problematic Internet use* (PIU) is characterized by excessive or poorly controlled preoccupations, urges, or behaviors regarding computer use and Internet access that lead to impairment or distress. This lesson reviews studies on the comorbidity of Internet addiction with psychiatric disorders in adults and adolescents over the period 2006–2015. Forty-three studies have been selected and evaluated. Cross-sectional studies on samples of patients have reported high comorbidity of Internet addiction with psychiatric disorders, such as affective disorders, anxiety disorders (including generalized anxiety disorder and social anxiety disorder), *attention-deficit hyperactivity disorder* (ADHD), drug and alcohol abuse, and personality disorders. A relationship between anxiety, depression, and future Internet addiction has been established. Depression and hostility aggravate Internet addiction in adolescents, and when there is a remission from Internet addiction, there is a decrease in depression, hostility, and social anxiety. No causal role has been established between Internet addiction and psychiatric comorbidity, but there is growing evidence that Internet addiction is a behavioral addiction, although the pathophysiological mechanisms underlying Internet addiction are still under investigation.

COMPETENCY AREAS: This lesson addresses the gap in learning in the areas of knowledge, diagnosis, treatment, and practice-based learning and improvement regarding Internet addiction. Many clinicians lack an understanding of how to adequately identify Internet and videogame addiction, which is also often underreported by adolescents and their families. Internet addiction co-occurs with several psychiatric disorders such as depression, anxiety, ADHD, drug and alcohol abuse, and personality disorders. After reading this lesson, readers will have a better understanding of Internet addiction and how to assess this disorder and comorbid psychiatric disorders.

Introduction to Internet Addiction

Problematic Internet use (PIU), or Internet addiction, is characterized by excessive use, impairment, or distress as result of the use of the internet. Early studies by Young,[1] Griffiths,[2-3] and Aboujaoude[4] defined this disorder and included extensive research on it. The condition has attracted increasing attention in the popular media and among researchers, and this increase in attention has paralleled the growth in computer use and Internet access.[5] **Phenomenologically, there appear to be at least three subtypes of Internet addiction: excessive gaming or gambling, sexual preoccupations (cybersex), and socializing or social networking including e-mail and text messaging.** Internet addicts may use the Internet for extended periods, isolating themselves from other forms of social contact, and may focus almost entirely on the Internet rather than on other life events. Adolescents with problematic Internet use showed dysfunctional coping strategies with problems in school and home and exhibited poor interpersonal relations.[6] Internet addiction can also be explained by a need to escape from oneself, which may account for the excessive playing of Internet games.[7]

Three different models have been proposed for PIU.[8-11] **Some researchers have considered impulse-control disorders as part of the obsessive-compulsive disorder spectrum as a model.** This model is supported by brain-imaging and pharmacological treatment studies with *selective-serotonin reuptake inhibitors* (SSRIs),[12] although other treatments and brain-imaging studies may challenge it. **PIU has also been conceptualized as an impulse control disorder, characterized by the urge to repeatedly engage in a behavior—going online—that is pleasurable in the moment but can lead to negative downstream effects.[4] Third, Internet addiction has been suggested for inclusion in the behavioral addiction spectrum because it involves excessive use despite adverse consequences, withdrawal phenomena, and tolerance, all of which characterize many substance-use disorders.** The frequent appearance of Internet addiction in the context of numerous comorbid conditions raises complex questions of causality.

Diagnosis and Clinical Criteria

Four components were originally suggested as essential to the diagnosis of Internet addiction for inclusion in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5):[13]

1. **excessive Internet use, often associated with a loss of one's sense of time or a neglect of basic drives;**
2. **withdrawal, including feelings of anger, tension, and/or depression, when the computer is inaccessible;**
3. **tolerance, including the need for better computer equipment, more software, or more hours of use; and**
4. **adverse consequences, including arguments, lying, poor school or vocational performance, social isolation, and fatigue.**

A major survey has aimed to develop diagnostic criteria for *Internet addiction disorder* (IAD) and evaluate their validity and reliability in the general population.[14] The diagnostic criteria include a symptom criterion (seven clinical symptoms of IAD), a clinically significant impairment criterion (functional and psychosocial impairments), a course criterion (duration of addiction lasting at least 3 months, with at least 6 hours of nonessential Internet usage per day), and an exclusion criterion (exclusion of dependency attributed to psychotic disorders). Internet addiction was recognized as a condition for further study in DSM-5 but not as a disorder. Internet gaming disorder, however, was included in the appendix of DSM-5, published in May 2013. Thus, DSM-5 still does not offer sufficient guidance on how to approach individuals with suspected Internet-related psychopathology or how to design or interpret research studies on this topic. Instead, clinicians and researchers have to rely on proposed definitions in addition to several screening and assessment instruments developed for PIU and problematic video game use. This work includes a literature review of articles on Internet addiction and comorbidity published between 2006 and 2015. Forty-three studies have been selected and evaluated.

Psychiatric Comorbidity

Cross-sectional studies on samples of patients report high comorbidity of Internet addiction with psychiatric disorders, such as affective disorders, anxiety disorders (including generalized anxiety disorder and social anxiety disorder), and *attention-deficit hyperactivity disorder* (ADHD). Floros[15] assessed the comorbidity of IAD with other mental disorders in a clinical sample of college students who presented for treatment of IAD. The clinical sample revealed a high percentage of comorbidity with Axis I and II disorders. Half of the sample (25/50) presented with comorbidity of another Axis I disorder and 38% (19/50) presented with a concurrent Axis II personality disorder. The majority of Axis I disorders (51.85%) were reported before the onset of IAD, 33.3% were reported after the onset, and 14.81% of the cases were unclear.

There is evidence on the co-occurrence of Internet addiction with depressive mood disorder in adults.[16-18] A single study on bipolar depression[19] screened a clinical sample of 368 treatment seekers for excessive to addictive Internet use for bipolar spectrum disorders. Comorbid bipolar disorders were more frequent in patients who met the criteria for Internet addiction (30.9%) than among the excessive users (5.6%). This subgroup showed heightened psychopathological symptoms, including substance use disorders, affective disorders, and personality disorders.

Anxiety disorder was found in several studies of adult problematic Internet users.[20-21] Weinstein[22] investigated the association between Internet addiction and social anxiety in two samples of 120 university students (60 males and 60 females in each sample). The results showed a correlation between Internet addiction and social anxiety in the two samples, with no difference in the level of Internet addiction between males and females. The results also showed no preference for social networks among participants with high levels of social anxiety. Furthermore, the results of the study support previous evidence on the co-occurrence of Internet addiction and social anxiety.

Weinstein[23] found an association between compulsive buying on the Internet and anxiety as well as obsessive-compulsive traits. The participants were 120 habitual (more than twice a week) shoppers (70 men and 50 women). Weinstein showed that the *Edwards Compulsive Buying Scale* measures were associated with the Spielberger trait, but not state anxiety measures. The Spielberger trait anxiety measures are also correlated with measures on the *Yale-Brown Obsessive-Compulsive Scale* (Y-Bocs). The link between behavioral addictions, such as Internet addiction and compulsive buying, and anxiety and obsessive-compulsive measures has therefore been established.

Among South Korean adolescents, Internet addiction has been associated with depression in one study,[24] and high levels of depression and suicidal ideation in another study.[25-26] ADHD symptoms, depression, social phobia, and hostility were high in adolescents with Internet addiction in Taiwan.[27-28] In a later study, Yoo[29] examined the factors influencing Internet addiction and mental health in a nationally representative sample of 74,980 Korean middle- and high-school students. The odds ratios for potential Internet addiction were higher in boys and girls who reported suicidal ideation, depressive mood, moderate or higher subjective stress, moderate or more happiness, or ever having engaged in problematic substance use. Excessive gaming was associated with severe depression, social phobia, and Internet addiction symptoms in Taiwan. Female online gamers had fewer weekly online gaming hours and a shorter previous online gaming history, but tended to have more severe somatic pain and social phobic symptoms.[30]

In Turkey, Bozkurt[31] investigated the prevalence and patterns of psychiatric disorders in young subjects with IAD. A sample of children and adolescents (mean age, 13.38 ± 1.79 years; 45 boys and 15 girls) had been referred to the Istanbul Medical Faculty Child and Adolescent Psychiatry Department. All subjects (100%) had at least one comorbid psychiatric disorder and 88.3% (n = 53) had at least two comorbid psychiatric disorders. The frequencies of the diagnostic groups were as follows: behavioral disorder (86.7%), anxiety disorder (71.7%), mood disorder 38.3)%), elimination disorder (26.7%), tic disorder (16.7%), and substance use disorder (6.7%). The most common psychiatric disorders were ADHD (83.3%), social phobia ,(35%) and major depressive disorder (30%). In Australia, King (32) assessed the clinical features of *pathological video gaming* (PVG) and PIU in a cohort of 1,287 South Australian secondary school students. Depression, panic disorder, and separation anxiety were most prevalent among adolescents

with PIU. Adolescents with PIU appear to be at greater risk of Axis I comorbidity than adolescents with PVG alone. In Germany, Fischer[33] investigated associations between Internet addiction and depression, deliberate self-harm, and suicidal behavior among a representative sample of 1,435 German adolescents. Risky and pathological Internet users showed significantly higher rates of depression, deliberate self-harm, and suicidal behavior compared to students whose Internet use was normal. The results suggest that in addition to pathological Internet use, risky Internet use is associated with symptoms of depression, self-harm, and suicidal behavior. **A few studies have investigated the relationships between the development of Internet addiction and comorbid psychiatric conditions. A relationship between anxiety, depression, and future Internet addiction among South Korean males has been established,[34] and an exacerbation of depression, hostility, and social anxiety in the process of acquiring Internet addiction among adolescents has been reported.[35] In contrast, depression, hostility, and social anxiety decreased in the process of remission. See Table 1 for a list of studies showing Internet addiction comorbidity with other psychiatric disorders and symptoms. The table separates the adult and adolescent studies.**

Relationship of Internet Addiction with Drug and Alcohol Use

Very few studies have examined the relationship between drug and alcohol use and Internet addiction. Subjects who used cannabis had a higher mean score on the *Internet Addiction Test* (IAT) in Finland.[36] In the United States, parental problem drinking was found to have a significant and direct effect on Internet addiction in boys but not in girls in early adolescence. Significant indirect effects of parental problem drinking on Internet addiction were apparent in the boys' anxiety, depression, and aggression and through the girls' family function and aggression.[37] Problematic Internet use was has also been associated with substance use among Greek adolescents on the island of Kos.[38] Adolescents who have used illicit substances and abused the Internet appear to share some personality characteristics, such as psychoticism. Finally, Internet addiction has been associated with harmful use of alcohol among Taiwanese students.[39] It is unknown whether Internet addiction and these comorbid disorders could be explained by shared risk factors or are best considered as secondary disorders. A further study on the association between Internet addiction and alcohol addiction has been reported.[40] Male inpatients in rehabilitation centers who met the criteria for comorbid Internet addiction (n = 71) were compared with a matched control group of male patients treated for alcohol addiction without addictive Internet use (n = 58). Comorbid Internet addiction was found to be associated with higher levels of psychosocial symptoms, especially depression, obsessive-compulsive symptoms, and interpersonal sensitivity. Moreover, patients with Internet addiction have met the criteria for additional mental disorders more frequently. They have displayed higher rates of psychiatric symptoms, especially depression, and might need additional therapeutic treatment.

Conclusions

It is debatable whether Internet addiction stands as its own diagnosis or should be considered a product of other existing disorders such as anxiety, depression, ADHD, or impulse control disorders. **The evidence collected so far shows that depression and hostility aggravate Internet addiction in adolescents, and when there is a remission from Internet addiction, there is a decrease in depression, hostility, and social anxiety, although no causal role has been established between Internet addiction and psychiatric comorbidity.**

About the Faculty

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Acknowledgements

Prof. Weinstein is supported by grants from the National Institute for Psychobiology, Israel, and the Israeli anti-drug authority.

Table 1:
Internet Addiction Comorbidity with Other Psychiatric Disorders and Symptoms in Chronological Order

Comorbid Clinical Diagnosis	Studies	Country
Adults		
Depression Depressive mood disorder Manic depression	te Wildt et al., (2007)[16] Morrison and Gore, (2010) [17] Liberatore et al., (2011) [18] Alavi et al., (2012) [21] Cho et al., (2013) [34] Wölfling et al., (2015) [19]	Germany UK Puerto Rico Iran South Korea Germany
Anxiety	Kratzer and Hegerl, (2008) [20] Alavi et al., (2012) [21] Cho et al., (2013)[34]	Germany Iran South Korea
Alcohol abuse	Yen et al., (2009) [39]	Taiwan
Alexithymia and child maltreatment	Yates et al., (2012) [41]	US
Impulse control disorders	Mazhari (2012) [42]	Iran
Aggression	Alavi et al., (2012) [21]	Iran
Adolescents		
Personality disorders: hypomania, dysthymia, obsessive compulsive, borderline personality disorder, and avoidant personality disorder	Bernardi and Pallanti (2009) [43] Floros et al., (2014)[15]	Italy Greece
Alexithymia, dissociative experiences, impulse dysregulation	De Berardis et al. (2009)[44]	Italy
Alexithymia	Dalbudak et al., (2013) [45]	Turkey
Dissociative symptoms	Canan et al., (2012) [46]	Turkey
Conduct disorder and hyperactivity	Kormas et al., (2011)[47] Bozkurt et al., (2013)[31]	Greece Turkey
Depression	Kim et al., (2006) [25] Ha et al., (2007) [24] Yen et al., (2007)[27] Xiuqin et al., (2010)[48] Morrison and Gore (2010) [17] Tsitsika et al., (2011)[49] Cheung and Wong (2011)[50] Guo et al., (2012) [51]* Fischer et al., (2012)[33] Park et al., (2013) [26] Bozkurt et al., (2013)[31] Yoo et al., (2014)[29]	South Korea South Korea Taiwan China UK Greece Hong Kong Hong Kong Germany South Korea Turkey South Korea
Social phobia	Yen et al., (2007)[27] Wei et al., (2012)[30] Bozkurt et al., (2013)[31] Weinstein et al., (2015)[22]	Taiwan Turkey Israel
Somatic pain	Wei et al., (2012)[30]	Taiwan
ADHD	Yen et al., (2007)[27] Yen et al., (2009)[28] Bozkurt et al., (2013)[31] Weinstein et al., (in press)[52]	Taiwan Turkey Israel
OCD	Xiuqin et al., (2010)[48]	China
Insomnia	Cheung and Wong (2011)[50]	Hong-Kong
Elimination disorder, tic disorder substance use disorder	Bozkurt et al., (2013)[31] Fisoun et al., (2012)[38]	Turkey Greece

*In children

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L003353

Multiple Choice Questions

37. According to the lesson, all of the following are believed to be possible models of *problematic Internet use* (PIU), *except*:

A. Obsessive compulsive disorder.

B. Impulse control disorder.

C. Behavioral addiction.

D. Personality disorder.

38. In the study by Bozkurt, which one of the following conditions was most frequently associated with Internet and videogame addiction in children and adolescents?

A. Depression

B. Behavioral disorder

C. Substance use disorder

D. Tic disorders

39. Which of the following psychiatric disorders has been frequently described as related to Internet addiction?

A. Depression

B. Anxiety

C. Attention-deficit and attention-deficit hyperactivity disorder

D. All of the above

40. Which of the following statements accurately describes the relationship between Internet addiction and comorbid psychiatric disorders?

A. Depression and hostility worsen Internet addiction in adolescents.

B. When there is a remission from Internet addiction, there is no change in depression, hostility, and social anxiety in adolescents.

C. A causal role is established between Internet addiction and psychiatric conditions in adolescents.

D. None of the above

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Best Practices in CME

Internet Addiction: Comorbidity with Psychiatric Disorders

By Aviv Weinstein, PhD

ID#: L003353

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

CME Lesson Overview

This lesson reviews the evidence on the comorbidity of Internet addiction with psychiatric disorders among adults and adolescents. Readers will review the evidence for comorbidity of Internet addiction with other psychiatric disorders and their relationship in the development of the disorder.

Key Point 1: Overview

Understanding of basic models of Internet addiction and issues in the diagnosis of the disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) will aid in recognition and detection of key symptoms.

Key Point 2: Comorbidity

Clinicians should assess for psychiatric comorbidity with disorders such as *attention-deficit hyperactivity disorder* (ADHD), *attention-deficit disorder* (ADD), depression, anxiety, substance use, and personality disorders.

Key Point 3: Identify Symptoms

Identification of symptoms such as anxiety, depression, *obsessive-compulsive disorder* (OCD), ADHD, as well as other psychiatric disorders in adults is key for treatment of comorbid psychiatric disorders. Clinicians should be able to identify these symptoms and make a proper diagnosis.

Key Point 4: Integration and Comorbidity, Development, and Treatment of Internet Addiction

Additional research is needed for the integration of the topic of comorbidity of Internet addiction with other psychiatric disorders, how they interact in the development of the disorder, and how this can affect treatment.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Treating Insomnia

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No commercial support was used in developing this CME lesson.

KEY WORDS: Insomnia • Treatment • Pharmacotherapy • Psychotherapy

LEARNING OBJECTIVES: Upon completion of this lesson, clinicians will be able to (1) recognize the necessity of treating insomnia, (2) identify the full spectrum of currently available medications for treatment of insomnia, (3) understand the role of nonpharmacological treatments for insomnia, (4) identify the primary components of cognitive behavioral therapy for insomnia, and (5) utilize essential pharmacological interventions in treating insomnia.

ABSTRACT: Sleep disturbances are so common that insomnia often goes unrecognized by clinicians. When recognized, the sleep disturbance is often disregarded as a symptom that will resolve itself with the treatment of a comorbid condition. For this reason, insomnia often goes untreated and negatively affects patients' health by causing or exacerbating their medical illnesses. Various treatment methods have proved effective in treating insomnia. In this lesson, the authors provide an overview of these treatment approaches and the research supporting their use and discuss any known risks and controversies associated with them.

COMPETENCY AREAS: This lesson addresses the necessity of pharmacological and nonpharmacological approaches to treating insomnia and provides an overview of the same.

Insomnia

Insomnia is one of the most prevalent health concerns worldwide. Up to 33% of the general adult population experiences some symptoms of insomnia,[1,2] while rates as high as 69% have been observed in primary care settings.[3,4] Approximately 6%–10% of the general population suffers from insomnia disorder,[2, 5-7] which has been linked to serious impairments to quality of life[8] and daily functioning,[9, 10] including impaired job performance, higher rates of absenteeism, and higher healthcare utilization.[10, 11] Furthermore, insomnia is a known risk factor for multiple medical (e.g., cardiovascular) disorders, mental health concerns (e.g., depression, anxiety, mania, suicide), and increased mortality.[12-16]

Despite its ubiquity, insomnia is one of the most commonly unrecognized and untreated disorders.[17] For example, estimates suggest that the *majority* of medical patients with insomnia are never treated for their insomnia.[11] It is likely that insomnia remains untreated precisely because of its ubiquity. Sleep disturbance is one of the most frequently occurring symptoms in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).[1] Therefore, physicians might incorrectly assume that insomnia will resolve itself after patients' primary comorbid conditions are treated.[18] However, insomnia persists in 59%–88% of patients treated for standard medical concerns and in roughly half of those treated for depression.[19, 20] Moreover, untreated insomnia can exacerbate psychiatric and other medical symptoms, complicate recovery, and place patients at risk for relapse.[21-25]

The DSM-5 classifies *insomnia* as a psychiatric disorder for which the predominant complaint pertains to sleep quantity or quality; it is associated with difficulty initiating and maintaining sleep and with early-morning wakening. **The sleep disturbance must cause significant distress or impairment, occur at least three nights per week, persist for three months or more, and occur despite adequate opportunities to sleep.** Lastly, such sleep disturbances must not be explicable by or occur exclusively during the course of another sleep–wake disorder, coexisting mental disorder, or medical condition and must not be attributable to the physiological effects of a substance.[1] Sleep initiation and maintenance difficulties are customarily operationalized with a sleep latency or midnight wakening period lasting 30 minutes or more.[26]

Comorbidities

Insomnia is usually seen in clinical settings as a comorbid condition.[1] It is both a risk factor for and cause of other medical disorders.[27-31] However, if not directly addressed, insomnia can prolong, exacerbate, and interfere with the treatment of other comorbid medical conditions.[32] Even when insomnia is clearly precipitated by another medical condition, the insomnia itself often persists if left untreated.[33]

Previous insomnia classifications distinguish between *primary* and *secondary* insomnia, such that primary insomnia is precipitated by another psychiatric or medical condition and secondary insomnia is precipitated by another medical condition.[34] Not only is it impossible to make this distinction at times, but such a differentiation is of little practical use.[35] Insomnia is often prolonged by factors other than the original precipitants.[36, 37] For this reason, insomnia can persist independent of treatment for the precipitating factor. Such perpetuating factors are often cognitive and behavioral and thus might not respond to traditional medical interventions. For example, while treatment for hyperthyroidism will address thyroid issues that have precipitated a sleep disturbance, it will not address the factors that perpetuate the subsequent insomnia, such as worry and napping. The *DSM-5* has thus discarded the distinction between primary and secondary insomnia and instead uses the umbrella term *insomnia disorder*.[1] Nevertheless, understanding insomnia's common comorbidities and their interplay with the disorder can be extremely useful.

Depression:

Sleep disturbance is one of the primary symptoms of *major depressive disorder* (MDD), occurring in roughly 80% of cases.[38,39] However, sleep disturbance and fatigue commonly linger after completion of treatment for major depression.[40] In fact, insomnia is the most common residual symptom of this comorbid condition, persisting in over 65% of individuals who have experienced first-onset depression.[41] This suggests that insomnia becomes an autonomous part of mood disturbance and demands its own direct

clinical attention. If left untreated, chronic insomnia can exacerbate mood problems and increase suicidal behavior.[25, 42-45] Conversely, successful treatment of insomnia has been shown to lessen the risk of depression.[46, 47]

Treatment of MDD with a combination of antidepressants and hypnotics has been shown to relieve both depressed mood and sleep disturbances more effectively when compared with antidepressant and placebo treatment.[48] This reveals how advantageous it is to classify and treat MDD and insomnia as distinct phenomena. Additionally, baseline depression levels do not impact the efficacies of *cognitive-behavioral insomnia treatments* (CBT-I).[49]

Anxiety:

It may be unsurprising that anxiety and insomnia feed into one another. Patients with anxiety are at 17 times greater risk of developing insomnia than those without anxiety.[50] Conversely, of those with insomnia, 44% are diagnosed with comorbid generalized anxiety disorder.[29] Anxiety plays a role in predisposing, precipitating, and perpetuating insomnia. Specifically, those with heightened basal anxiety and arousal levels are at increased risk for developing insomnia.[51] Moreover, acute stress and anxiety can also lead to episodes of insomnia. Worse still, those who attempt to "will" themselves to sleep often experience *sleep performance anxiety*, which perpetuates their difficulty sleeping.[52] Clearly, anxiety predisposes individuals to insomnia. However, evidence also suggests that insomnia leads to increased daytime anxiety and worry.[53-55] Thus, the relationship between insomnia and anxiety is reciprocal.

Chronic Pain:

Sleep disturbances occur in 50%–88% of patients experiencing chronic pain.[55-60] Chronic pain has been associated with increased sleep latency and total wakefulness, prolonged awakenings, and decreased total sleep time and efficiency.[61, 62] Not only does pain lead to sleep disturbances, though, but disturbed sleep has also been shown to increase pain over both short- and long-term intervals.[63-66] Additionally, sleep deprivation has been shown to cause enhanced pain sensitivity in healthy individuals,[67, 68] again suggesting a reciprocal relationship between insomnia and pain disorders.

The above is, by far, not an exhaustive list of medical conditions comorbid with insomnia; it does not, for instance, discuss psychotic disorders, thyroid dysfunction, other sleep and sleep–breathing disorders, and many other possible comorbid conditions. Suffice it to say, then, that a specialist referral is warranted for appropriate evaluation and treatment if a patient is suspected to have an underlying comorbid medical condition. As for treating insomnia itself, there are a number of options.

Pharmacological Insomnia Treatments

Insomnia is most often treated pharmacologically. Certainly since the dawn of civilization and likely before, humanity has used a multitude of hypnotics to induce sleep. Plants, animal parts and secretions, minerals and synthesized organic substances, and finally, the complex medications that have advanced significantly in the past century and are regulated as part of today's billion-dollar pharmaceutical industry have all been administered to the same ends. The *American Academy of Sleep Medicine's* (AASM's) latest clinical guidelines for the pharmacological treatment of insomnia were developed and published in 2008.[69] Since that time, new hypnotics have been designed and approved, and a more robust body of scientific literature on the use of hypnotics has been published. What is now certain is that several neurotransmitters are involved in regulating the sleep–wake cycle:

- **GABA (γ-aminobutyric acid)**
- **Histamine**
- **Melatonin**
- **Orexin**
- **Serotonin**

There are hypnotics available that act on each of the above receptor classes, and some act on several receptor classes simultaneously. They are usually prescribed for use 30 minutes before bedtime and all can cause daytime sedation.

GABA Agonists:

Benzodiazepines

Medications in this class of hypnotics are not recommended as first-line or long-term treatments for chronic insomnia due to their many adverse side effects, including daytime somnolence, cognition and memory impairment, increased risk of falling, respiratory suppression, sleep-architecture (*Rapid Eye Movement* [REM] sleep) suppression and degradation, high addiction potentiality, rebound insomnia, and anxiety. All medications in this class are schedule IV controlled substances. They are, however, useful as short-term insomnia treatments (7–10 days). The following medications belong to this class and differ in their half-lives, the significance of which will be discussed below.

Table 1:
Benzodiazepines

Medication	Trade Name	Dosage Recommendation
Estazolam	Prosom	0.5–2 mg
Flurazepam	Dalmane	15–30 mg
Triazolam	Halcion	0.125–0.5 mg
Temazepam	Restoril	7.5–30 mg

Other benzodiazepines commonly used as off-label medications in treating insomnia include *lorazepam* (Ativan), *clonazepam* (Klonopin), *alprazolam* (Xanax), *diazepam* (Valium), and *oxazepam* (Serax). The use of these medications in treating insomnia is controversial, and there is no conclusive evidence supporting their use in this context.

Non-Benzodiazepines

Like benzodiazepines, these medications are GABA-A modulators, but non-benzodiazepines are more selective and do not cause high levels of tolerance, dependence, or withdrawal. They might also be preferred over benzodiazepines because of their rapid activations, the short durations of their effects, and their safety profiles. Yet, despite these highly positive features, they are still controlled, schedule IV substances.

Zolpidem (Ambien) and Zolpidem CR (controlled release)

The difference between these two medications lies primarily in their half-lives, as discussed below. They were two of the most commonly prescribed insomnia medications during the first decade of the present century, yet newer hypnotics have since been shown to have better safety profiles, making the latter more popular as insomnia treatments of late.

- **Dosage:** 5–10 mg (6.25–12.5 for CR)
- **Adverse side effects:** Somnolence, dizziness, ataxia, amnesia, complex sleep-related behaviors, rebound insomnia.[69]

Zaleplon (Sonata)

In one meta-analysis, zaleplon was proven effective and safe for treating insomnia.[70] Nevertheless, its use among clinical practices has been limited, primarily because of its ultrashort half-life.

- **Dosage:** 5–20 mg
- **Adverse side effects:** Somnolence, dizziness, ataxia, amnesia

Eszopiclone (Lunesta)

Eszopiclone is the best-documented agent in terms of safety for long-term use and has little or no suggestion of increased tolerance, dependence, or abuse. It might even be safe to use in patients who have histories of substance abuse yet require hypnotic treatment.[71]

- **Dosage:** 1–3 mg
- **Adverse side effects:** Somnolence, amnesia, ataxia, dizziness, dry mouth, and unpleasant taste in the mouth

Histamine Antagonists

Diphenhydramine (Benadryl)

This is a classic antihistamine. Its sedative properties are attributed to its antagonistic action on H1 histamine receptors. Diphenhydramin is not approved by the *U.S. Food and Drug Administration* (FDA) for insomnia

treatment, and its efficacy is controversial; however, in low doses it is widely used and prescribed as an over-the-counter and prescription sleep aide.

- **Dosage:** 25–50 mg
- **Adverse side effects:** Sedation, dizziness, constipation, nausea, dry mouth, blurred vision, weight gain
- **Serious side effects include:** Urine retention, cardiac arrhythmia, confusion, bowel obstruction
- **Note:** This medication is not recommended by the AASM for treatment of chronic insomnia due to the relative lack of efficacy and safety data.[69]

Tricyclic Antidepressants

In low doses, tricyclic antidepressants have been used as sleep aides for many years. Their affinity to H1 histamine receptors and their 5HT2 receptor antagonism appear to have synergistic, sleep-promoting effects.

Doxepin (Silenor)

In low doses, *doxepin* is the first and only FDA-approved insomnia medication in its class, and it is not a controlled substance. While high doses of ***doxepin can be detrimental***, low doses appear to be safe and have proven effective at inducing sleep with few side effects.[73] **Furthermore, doxepin is the only hypnotic medication specifically tested and approved to use in treating insomnia in geriatric patients.**

- **Dosage:** 3–6 mg
- **Adverse side effects:** Somnolence, nausea
- **Note:** Doxepin may be preferred over other sleep aids due to its very low side-effect profile and is especially helpful in treating geriatric patients for whom it is the only FDA-approved insomnia medication.

Other medications in this class have been widely used in treating insomnia, but have not received FDA approval. These medications were especially popular as alternatives to benzodiazepines prior to the development of non-benzodiazepine hypnotics. The most commonly used medications of this kind are *amitriptyline* (Elavil) and *nortriptyline* (Pamelor), both in doses of 10–25 mg. There is a dearth of studies showing adverse effects for low doses of tricyclic antidepressants.

Other Sedative Antidepressants

Mirtazapine (Remeron)

Mirtazapine is an antidepressant featuring both a high affinity to H1 histamine receptors and 5HT2 receptor antagonism. This appears to contribute to its sleep-promoting properties.[73]

- **Dosage:** 7.5–15 mg
- **Adverse side effects:** Somnolence, increased appetite and weight gain, abnormal dreams, dizziness, dry mouth, constipation, seizures (rare)

Trazodone (Desyrel)

Even in low doses, this medication saturates both H1 histamine and 5HT2A receptors, making it a potent hypnotic. It is extensively used among clinical practices in treating insomnia despite its lack of FDA approval for use as a sleep medication.[74]

- **Dosage:** 25–150 mg
- **Adverse side effects:** Somnolence, dry mouth, orthostatic drop in blood pressure causing dizziness, blurred vision, constipation, priapism (rare), and seizures (rare)

Sedating Antipsychotics

Quetiapine (Seroquel)

In addition to offering H1 antagonism, quetiapine is also a 5HT2A receptor antagonist, adding to its sedative effects. It is widely used as an off-label medication in treating insomnia; however, there are very few studies evaluating its efficacy and safety in this context.[75]

- **Dosage:** 12.5–50 mg
- **Adverse side effects (low doses):** Although there is an overall of lack evidence, weight gain has been mentioned.[76-78]

Olanzapine (Zyprexa)

Olanzapine has the highest affinity to H1 receptors of any atypical antipsychotic[79] and has been shown to improve slow-wave sleep.[80] This is likely because of its 5HT2 antagonism.[73] Despite these seemingly positive features, however, olanzapine is not a commonly prescribed insomnia medication for patients who do not suffer from psychiatric disorders. This is likely due to its notorious metabolic side effects, including weight gain and metabolic syndrome.

- **Dosage:** 2.5–5 mg
- **Adverse side effects (low dose):** Although there is an overall of lack evidence, somnolence and metabolic disorder are sporadically mentioned.

Melatonergic Hypnotics

Melatonin

Melatonin and ***ramelteon*** (Rozerem)—the latter of which is a melatonin receptor agonist—are both effective at inducing sleep onset rather than sleep maintenance. Melatonin is a melatonin 1 and 2 receptor agonist. In the USA, melatonin is only available as an over-the-counter supplement and is not approved by the FDA for use in treating insomnia. Moreover, its dosage is not always reliable. Nevertheless, it is widely used and often preferred as a first-line treatment for insomnia due to its low side-effect profile.

- **Dosage:** 1–10 mg
- **Common side effects:** Daytime sleepiness, dizziness
- **Note:** Although melatonin can be responsible for a 40%–50% decrease in circadian body temperature, this drop is clinically insignificant.[81,82]

Ramelteon (Rozerem)

A melatonin 1 and 2 receptor agonist, ***ramelteon*** is FDA-approved for treating insomnia. According to several meta-analyses, short-term ramelteon use is associated with improved sleep parameters in patients with insomnia, but its clinical impact is deemed small. That said, as it has a relatively low side-effect profile, ***ramelteon*** is often preferred over benzodiazepine and non-benzodiazepine GABA agonists. However, there is presently a lack of long-term trials.[83]

- **Dosage:** 8 mg
- **Adverse side effects:** Somnolence, dizziness, fatigue

Orexin Antagonists:

Suvorexant (Belsomra)

Investigations into pharmacologically blockading orexin receptors have led to this medication's development and FDA approval for treating sleep-onset and sleep-maintenance insomnia. **Suvorexant, a dual antagonist of orexin 1 and orexin 2 receptors, does not induce sleepiness but decreases wakefulness, which makes it a unique sleep agent in terms of today's market.** It has been proven safe and effective for over one year of nightly use and is indicated for long-term use. Additionally, there is no evidence that its prolonged use causes physical dependence, nor have any withdrawal symptoms been reported in cases when its use has been discontinued.[84, 85] Overall, it is highly effective and has few side effects, making it a preferred choice among prescribing physicians since its February 2015 release. Nevertheless, it remains a schedule IV federally controlled substance.

- **Dosage:** 5–20 mg
- **Adverse side effects:** Somnolence, confusion, complex sleep-related behaviors, abnormal dreams

Serotonin System:

Blockading 5HT2A receptors has been strongly associated with promoting sleep, and many medications that provide such blockades are used in treating insomnia. Still, none of the medications used in this way are pure 5HT2A antagonists, and all share affinity to histamine H1 receptors, as described above. Currently, no FDA-approved medications for treating insomnia act solely on serotonin receptors.

Understanding and Utilizing Medication Half-Lives in Treating Insomnia:

In *Disorders of Sleep and Wakefulness and their Treatment,*[71] the importance of hypnotics' half-lives is discussed, and it is suggested that this can have an important impact on medications' tolerability and efficacy profiles. In this vein, four medication classes are outlined:

1. **Hypnotics with ultra-long half-lives** (>24 hours: flurazepam [e.g., Dalmane, Dallmadorm]) can cause drug accumulation with chronic use. This can cause impairment, which has been associated with increased risks of falling, particularly among the elderly.
2. **Hypnotics with moderate half-lives** (15–30 hours: *estazolam* [Prosom], *temazepam* [Restoril], most tricyclic antidepressants, mirtazapine, olanzapine) might not wear off until after the individual needs to awaken and thus can have "hangover" effects (e.g., sedation and memory issues).
3. **Hypnotics with ultra-short half-lives** (1–3 hours: *triazolam* [Halcion], zaleplon, zolpidem, melatonin, ramelteon) can wear off before the individual needs to awaken and thus cause loss of sleep maintenance.
4. **Hypnotics with half-lives that are short but not ultra-short** (approximately 6 hours: zolpidem CR, low doses of trazodone, quetiapine, doxepin, diphenhydramine) can provide rapid-action onset and plasma levels above minimally effective concentrations only for the duration of a normal night's sleep.

Nonpharmacological Approaches

Repetitive Transcranial Magnetic Stimulation (rTMS):

This procedure uses an electromagnet to generate electric currents that stimulate areas of the brain. It has been used successfully as an adjuvant therapy in treating depression.[86] Promising new research on the use of rTMS in treating insomnia has recently come to light.[87]

Cranial Electrotherapy Stimulation (CES):

This has also been shown to yield positive results in the treatment of insomnia. Like rTMS, CES uses a small device to send weak electrical pulses to desired areas of the brain. It has been approved by the FDA for use in treating anxiety, depression, and insomnia since 1979. A meta-analysis of 20 studies has shown there is a strong combined effect size for CES in treating insomnia, with few negative side effects, and its use has also been shown to precipitate fast (as little as one week), significant improvements to sleep behaviors.[88]

Light Exposure:

Although often subsumed under the umbrella of cognitive behavioral therapy for insomnia or CBT-I (i.e., sleep hygiene), light exposure has been used independently to treat insomnia, particularly with patients suffering from circadian rhythm disturbances. Light is a primary cue to which the human circadian clock is attuned. Humans typically receive exposure to light during the daytime and are less exposed to light at night, thereby inducing wakefulness during the day and drowsiness at night. For those whose sleep patterns are misaligned with their desired sleep patterns, light exposure can provide a solution. Exposure to natural or artificial light can be used to strengthen or reestablish a desired circadian rhythm. Exposure to bright light and the avoidance of light during predetermined times of day can be used to improve sleep and occupational functionality for nightshift workers.[89-90] Nurses who work rotating shifts, for example, have exhibited significant improvements in their sleep quality after exposure to artificial bright light when they avoid daytime sun exposure.[91]

Meditation:

Mindfulness meditation is a process during which one focuses one's attention on the present moment without judgment.[92] Mindfulness practices are often incorporated in relaxation training, a component of CBT-I.[93] However, meditation is still considered an autonomous technique for treating insomnia. A recent randomized control trial utilizing mindfulness meditation showed improvements in patient total wakefulness and physiological arousal.[94] Mindfulness meditation can also be effectively used in conjunction with CBT-I.[95]

Psychotherapeutic Treatments

Psychology's understanding and treatment of insomnia using psychotherapy have evolved considerably since the field's inception. While early psychoanalytic writings accurately predicted (in more abstract terms) what contemporary researchers have only recently demonstrated, they also made some wildly idiosyncratic and recondite predictions. For example, Sigmund Freud recognized the roles of worry and arousal in thwarting sleep when he described the "lowering of the [mental] censorship at night that the forbidden wishes have to thank for being able to become active once more."[96] However, drawing from his theories of unconscious sexual drives, Freud also posited in a case study that "there can be no doubt that sexual satisfaction is the best soporific," and blamed a lack of sexual intercourse for the sleep difficulties his male patient was suffering.[97]

The rise of behaviorism in the 1940s led psychology away from abstract interpretations and toward objective, measurable, and observable phenomena, eventually spawning early forms of *cognitive behavioral therapy* (CBT). Customarily, CBT emphasizes the present (rather than the past), observable and measurable behaviors, the importance of environmental influences, empirical research methods, and the use of outcome measurements. CBT-I is an amalgamation of techniques from multiple fields, all of which focus on promoting changes in cognition, behavior, environment, and physiology. Mindfulness practices, for example, are derived from traditional Buddhist practices but have recently been incorporated into CBT-I as means of reducing physiological arousal and counterproductive thought patterns. The most common interventions incorporated into CBT-I practices are stimulus control, cognitive, and sleep restriction therapies, sleep hygiene, and relaxation training.[98-101] These techniques are discussed in greater detail in the following sections.

The vast majority of research into psychotherapeutic treatments for insomnia has examined CBT-I. Furthermore, originally autonomous techniques with demonstrable efficacies in the treatment of insomnia have also subsumed into CBT-I. For these reasons, therapeutic alternatives to CBT-I are few, and further data is needed to provide convincing substantiation of such alternatives' efficacies. There are, however, various approaches that have shown promise. Hypnotherapy, which has been used to treat insomnia since as early as 1906,[102] typically relies on a specially trained hypnotherapist to induce trance-like relaxation states using guided imagery. More recent clinical trials examining hypnotherapy have demonstrated improvements in total sleep time and quality and in the number of awakenings.[103-105] Meanwhile, interpersonal psychotherapy, which focuses on the development of healthy social interactions as means of regulating emotions, has been shown to improve total sleep time and efficiency and to lessen wakefulness after sleep onset in patients with primary insomnia.[106] Finally, research into *acceptance and commitment therapy* (ACT), a third-wave CBT approach that encourages committed action and acceptance of displeasing experiences, has been shown to yield improvements in quality of life for sufferers of primary insomnia.[107]

CBT-I:

CBT-I is a specially designed insomnia treatment approach. It consists of empirically validated interventions targeting the various factors that perpetuate insomnia. As it has proved effective in many clinical trials, the American Academy of Sleep Medicine recommends CBT-I as a standard treatment for chronic insomnia.[108]

CBT-I's Efficacy

CBT-I has proved effective in both individual and group treatment settings[109, 110] and in self-help and in-person modalities[111] in as few as two sessions.[112, 113] Outcome measures typically examine *sleep onset latency* (SOL), *waking after sleep onset* (WASO), *total sleep time* (TST), and sleep efficiency. (For a list of definitions and abbreviations, see Table 2.) Studies commonly show CBT-I yields a 50%–60% reduction in SOL and WASO[17] of nearly 30 minutes for each. Likewise, TST typically increases on average by about 30–45 minutes, and sleep efficiency improves by 85%.

Table 2:
Sleep Outcomes

Outcome	Abbreviation	Definition
Sleep onset latency	SOL	The amount of time it takes for an individual to transition from wakefulness to sleep
Waking after sleep onset	WASO	The amount of time an individual spends awake between sleep onset and final awakening
Total sleep time	TST	The total amount of time spent asleep
Time in bed	TIB	The total amount of time spent in bed per night
Sleep efficiency		The number attained after dividing TST by TIB

Not only has CBT-I proven efficacious, but patients with chronic insomnia typically prefer it over pharmacological treatments.[7, 23, 114, 115] CBT-I does indeed pose several advantages over psychopharmacological approaches, insomuch as it has fewer known side effects and allows patients to directly change the factors perpetuating their sleep disorders. It has also proved as effective as pharmacotherapy as a short-term insomnia treatment, and many studies have shown it is *more* effective for long-term treatment.[23, 44, 99]

CBT-I has also proven effective as a treatment for comorbid insomnia and in some cases reduces symptoms of the comorbid condition as well. Among chronic pain sufferers with comorbid insomnia, CBT-I has not only proven effective at improving SOL and WASO but has reduced pain sensitivity.[116] In individuals exhibiting residual symptoms of both depression and insomnia following "adequate" psychiatric treatment, CBT-I yielded significant reductions in both disorders, and these reductions persisted, even after the end of treatment.[117]

Conceptualization

Cognitive-behavioral conceptualizations of insomnia posit that insomnia, though often precipitated by acute events or life changes, is ultimately the result of maladaptive, compensatory reactions (i.e., thoughts and behaviors) to an initial loss of sleep.[118, 119] For example, an individual who recently underwent hip surgery might have initially experienced difficulty sleeping due to pain from surgery. However, the insomnia then continues when said individual attempts to compensate for the resulting daytime sleepiness by taking short naps throughout the day. The disruptions to the individual's sleep–wake routine caused by daytime napping reduce the probability of this individual sleeping throughout the night. Furthermore, maladaptive cognitive habits, such as concerns over losing sleep, can lead to states of arousal that are incongruent with falling asleep. Should this individual's thought patterns and sleep habits remain unchanged, it is likely the insomnia will linger despite the fact that the post-surgery discomfort that precipitated it has ended. CBT-I therefore incorporates interventions designed to mitigate these perpetuating factors.

Stimulus Control Therapy

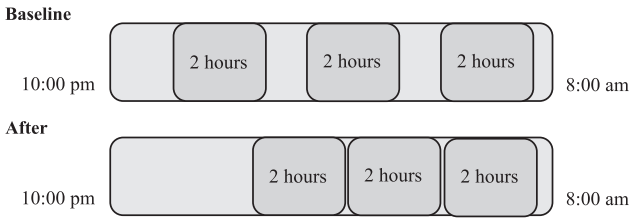
***Stimulus control therapy* (SCT)[120] is often considered a first-line insomnia treatment, as it is an intervention designed to strengthen the association between the patient's bed and sleep.** Over time, the patient begins to associate the bed, bedroom environment, and nighttime rituals with rapid sleep onset. Fundamentally behavioral in nature, SCT relies quintessentially on classical conditioning, such that the neutral stimulus of a bed is paired with the unconditioned stimulus of sleepiness. In SCT, patients are instructed to: (1) only go to bed when tired, (2) only use the bed for sleep, (3) move out of bed if unable to sleep within 10–15 minutes, (4) get up at the same time each morning, and (5) only sleep in the bed.[121] Less common SCT techniques include instructing patients to leave the bed if feeling aroused (e.g., angry, frustrated, anxious) and to return only when feeling tired, to implement pre-bed rituals (e.g., showering 45 minutes before bedtime), and to incorporate relaxation techniques while in bed or the bedroom. With

repetition, the patient's association between the bed and drowsiness are strengthened, and the patient begins to exhibit a conditioned response (i.e., sleep) in the presence of the conditioned stimulus (i.e., the bed) alone. That is to say, the patient will begin to feel sleepy when entering the bed and will fall asleep quickly.

Sleep Restriction Therapy

Sleep restriction therapy **(SRT)[119] also strengthens the association between bed and sleep and, furthermore, maximizes the patient's desire for sleep by restricting sleep opportunities.** Those with insomnia often present with extremely low sleep efficiencies; that is, they spend large amounts of time awake in bed. Sleep efficiency is calculated by dividing *total sleep time* (TST) per night by *time in bed* (TIB). SRT reduces a patient's TIB so it equals their average TST per night. One of SRT's initial goals is to improve sleep efficiency. By restricting sleep opportunities to a limited timeframe, sleep becomes more consolidated. That is, periods of wakening during the night become shorter in duration and less frequent (see Table 3).

Table 3:
Sleep Consolidation



Perhaps unsurprisingly, patients tend to favor stimulus control over sleep restriction.[115] For instance, a patient might voice concerns regarding the irony of seeking treatment for insomnia and being asked to reduce the amount of time spent in bed. First, the clinician must assuage these concerns by validating them; then, the clinician must motivate the patient to change their habits and promote the powerful effects of an SRT intervention. Next, the clinician, typically through the use of a patient sleep log, should calculate the patient's TST. The clinician should then work with the patient to set a fixed wake time and to decrease TIB to a number equal to the patient's TST. Customarily, however, TIB is never reduced by less than 4.5 hours. Utilizing the agreed upon fixed wake time and TST, the patient's bedtime is set such that TIB is equal to TST. Bedtime is delayed, as opposed to wake time being advanced, to take advantage of the increasing biological desire for (i.e., circadian predisposition to) sleep. Patients maintain the set sleep schedule weekly until sleep efficiency is increased to a preset percentage (typically 90%), in which case TIB is then titrated upward by 15 minutes until the desired sleep efficiency is again met. Standard procedures dictate that TIB be titrated downward if a sleep efficiency of at least 85% is not met and that it be maintained if sleep efficiency falls between 85% and 90%.

Sleep Hygiene

Sleep hygiene[122] is a form of psychoeducation regarding insomnia that serves to reduce or eliminate behaviors that are counterproductive to good sleep. It involves didactic instruction on beneficial behaviors and their rationales, often accompanied by a handout containing details. Examples of standard sleep hygiene items include (1) waking at the same time each day, (2) exercising regularly, (3) reducing caffeine intake, (4) reducing clock checking, (5) eating regular meals, and (6) avoiding naps. Many of the items discussed as part of a sleep hygiene education program are designed to address the counterproductive, compensatory behaviors often adopted by those with insomnia to reduce daytime sleepiness (e.g., increased caffeine intake) or to catch up on sleep (e.g., taking naps).

Cognitive Techniques

Cognitive CBT-I techniques are used to address maladaptive beliefs or thought patterns that interfere with sleep. Individuals with insomnia are prone to certain cognitive tendencies (e.g., selective attention, worry) and maladaptive cognitions (e.g., believing that daytime problems are the result of poor sleep).[26] In fact, the *Dysfunctional Beliefs and Attitudes about Sleep* (DBAS) scale was developed to help clinicians identify patients' sleep-interfering cognitions.[26] The provider might address these maladaptive cognitions through a variety of cognitive interventions, such as evidence gathering, thought logs, or behavioral experiments.

Case Example

> Jane has had difficulty sleeping ever since starting her new job, which is stressful in its own right, but also requires that she wake up an hour earlier than she had in the past. She feels pressured to perform well in her new position, but since the shift in her sleep schedule, she has had difficulty focusing in the mornings. She worries she will make errors at work and her supervisor will fire her. To ensure she gets enough sleep, Jane has been going to bed *two* hours earlier than normal each night. While she falls asleep immediately, she typically wakes up two hours later, frustrated, unable to return to sleep, and worrying continually about her job performance. She tells herself, *"If I don't get to sleep by 11:00, I will be useless tomorrow."*

Jane's insomnia is prolonged, in part, by her belief that her sleep difficulties will affect her daytime functionality to the extent that she will be fired. It is possible that Jane is overestimating her daytime impairment, is misattributing her impairment to her sleep difficulties, or is overestimating her boss's reaction to her daytime impairment. However, because of her belief, Jane has attempted to compensate for her daytime sleepiness by further disrupting her sleep routine (i.e., going to bed earlier). She spends her time in bed worrying, which increases her physiologic arousal, decreases her likelihood of falling asleep, and strengthens the association between her bedroom and states of arousal. A clinician working with Jane might attempt to challenge her maladaptive beliefs by first encouraging Jane to gather evidence, perhaps by asking her supervisor for feedback on her job performance. The clinician can then encourage Jane to replace her original thoughts with those that incorporate *all* the evidence Jane has gathered, rather than only considering evidence that supports her maladaptive beliefs. One example of a more accurate, helpful thought might be "*Even when I have some trouble concentrating, I usually do a good job*."

Individuals with insomnia are often worriers, particularly with regards to sleep.[123, 124] Worry is conceptualized as an avoidance strategy (whereby individuals attempt to avoid displeasing emotional experiences) and a misguided attempt to solve a problem cognitively.[125] Just like other compensatory mechanisms, worry serves the opposite of its intended function, in this case by increasing autonomic activation, thereby decreasing the likelihood of sleep.[123, 126] Worry logs are often used in CBT as an intervention to target worry. Individuals with insomnia might lie down to sleep only to experience intrusive and repetitive thoughts that initiate an arousal response (i.e., worry). This repetitive thought cycle continues, often in an attempt to solve the problem, leading to increased levels of arousal. However, bed is hardly the place to solve problems. To help patients suppress these repetitive thoughts, clinicians should encourage them to keep logs next to their beds and to record any thoughts they have so they can return to them later. This intervention can be used in conjunction with "worry time," a designated period each day in which patients allow themselves to worry; this latter intervention entails postponing all worries until "worry time" and otherwise avoiding worry at other times. Using this technique, patients are often able to purge themselves of the need to worry altogether.

Relaxation Training

Relaxation training[127, 128] is designed to reduce both physiological and cognitive arousal states that are incompatible with sleep. Relaxation training typically consists of four components: (1) breathing, (2) progressive muscle relaxation, (3) autogenic training, and (4) imagery.[114] Patients learn these skills during therapy and are encouraged to practice them during the intervening week, both during the day and before bedtime. Patients might also use audio recordings of relaxation instructions or guided imagery scripts to help them implement these skills.

Difficulties

CBT-I is demanding on patients. Individual and group (as opposed to online or self-help) CBT-I not only requires patients to visit therapy offices weekly, but requires they arrive punctually, stay awake, interact with others, implement significant lifestyle changes, log their sleep, and practice techniques outside of therapy. This can be very demanding for individuals already experiencing daytime sleepiness and diminished functionality, and it is *especially* demanding for those with a comorbid

condition like chronic pain or depression. For this reason, attrition rates for CBT-I can be high.

Non-completion rates for CBT-I have been noted as 13.7%–34% in six-session group settings,[129, 130] 30% for individual CBT-I,[131] and 9.7%–38.5% in sleep clinics.[115, 131-133] A recent meta-analysis showed comparable dropout rates for therapist-administered CBT-I and self-help CBT-I (CBT-I via booklet, videotape, audiotape, or the Internet), with average dropout rates of 16.7% and 14.5%, respectively.[134]

Drawbacks and Contraindications

Heide and Bokovec[135] identified the paradoxical phenomenon of relaxation-induced anxiety, whereby individuals provided with training in progressive relaxation and mantra meditation experienced anxiety as a result. It is estimated that roughly 15% of individuals receiving relaxation training will experience this effect. Individuals who suffer from nocturnal panic might be particularly susceptible to relaxation-induced anxiety.[136]

Meanwhile, SCT requires patients leave their beds within 15 minutes if not asleep. This instruction can be particularly difficult to follow for individuals with restricted mobility and chronic pain, as well as for those who have pronounced risks of falling (e.g., orthostatic hypotension). Additionally, SCT and SRT often result in an initial loss of sleep. Consequently, they can exacerbate daytime sleepiness, thus impairing judgment, aggravating pre-existing conditions like bipolar disorder and epilepsy,[137-139] and increasing risks of injury while driving and operating machinery.

Conclusion

Despite being one of the most prominent health concerns worldwide, insomnia is often overlooked and untreated. Insomnia has been linked to impairments in daily functionality and puts patients at risk for various medical and mental health problems. Two reasons insomnia is often overlooked and untreated are (1) it is frequently comorbid with other medical conditions and (2) care providers often have the misconception that insomnia will resolve itself if other medical conditions are effectively treated. However, insomnia often exacerbates coexisting medical conditions' symptomologies and interferes with their treatment. Further, it often persists independent of its precipitating factors. For these reasons, insomnia should be treated directly and quickly. Insomnia treatment has evolved tremendously over the past decade, and a variety of effective treatment options are now available. The variety of medications with different action mechanisms and the wealth of nonpharmacological modalities that can be used to treat insomnia allow clinicians to more specifically target insomnia in individual patients, thereby ensuring better outcomes. Treatment selection requires a thorough understanding of insomnia's etiology, progression, and comorbid conditions, as well as of each patient's lifestyle constraints, before a physician can select the best possible pharmacological approach. In addition to pharmacology, psychotherapeutic approaches have proven effective as both adjunct and stand-alone treatment options for chronic insomnia.

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Multiple-Choice Questions

41. For a diagnosis of insomnia, the sleep disturbance must:

A. last longer than six months.

B. cause significant distress or functional impairment.

C. occur exclusively.

D. predate a comorbid medical condition.

42. All the following are common elements of *cognitive behavioral treatment for insomnia* (CBT-I), *except*:

A. stimulus control therapy.

B. sleep restriction therapy.

C. rTMS.

D. relaxation training.

43. The only medication that decreases wakefulness rather than inducing sedation is:

A. doxepin.

B. suvorexant.

C. ramelteon.

D. mirtazapine.

44. Approximately 15% of those practicing relaxation training experience which of the following side effects?

A. Nocturnal enuresis

B. Muscle pain

C. Headache

D. Relaxation-induced anxiety

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Best Practices in CME

Treating Insomnia

By Vladimir Bokarius, MD, PhD; and Simon N. Ferber, MA

ID#: L003354

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium knowledge and daily practice.

Overview Head

Sleep disturbances are so common that insomnia often goes unrecognized and untreated by clinicians, and hence, negatively affects patients' health by causing or exacerbating their medical illnesses. Various treatment methods have proved effective in treating insomnia. This lesson provides an overview of current treatment approaches and the evidence supporting their use. The lesson also discusses known risks and controversies associated with treatment of insomnia.

Key Point 1: Assessment and Treatment Planning

Insomnia disorder often occurs autonomously and persists independent of its precipitating factors. For this reason, insomnia should be assessed in patients with sleep disturbances. If the necessary criteria are met, insomnia should be treated immediately.

Key Point 2: Psychopharmacological Treatment

A large variety of hypnotics are available today, providing clinicians with the ability to specifically target individual patients' insomnia while remaining sensitive to any comorbidities and environmental factors that might affect treatment. New developments in pharmacology for insomnia have enabled clinicians to prescribe effective insomnia medications with low side-effect profiles, regardless of the patient's age.

Key Point 3: Psychotherapeutic Treatment

CBT-I is considered the "gold standard" in psychotherapeutic treatment for insomnia and has been proven more effective than pharmacotherapy in long-term insomnia treatment. CBT-I works by addressing poor sleep hygiene, building a Pavlovian association between the patient's bedroom and sleep, developing the patient's relaxation skills, and reducing thoughts that interfere with sleep.

Key Point 4: Precautions

The insomnia treatment can pose a risk for some patients. For example, individuals with preexisting conditions like chronic pain, restricted mobility, epilepsy, and bipolar disorder, as well as those at risk of falling, might not be ideal candidates for sleep restriction therapy and might require a thoughtful choice of hypnotics. Risk factors should be assessed prior to treatment, and treatment should be adapted to minimize risk to the patient.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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The Mental Health Sequelae of Major Disasters

Carol S. North, MD, MPE

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

KEY WORDS: Disaster • Posttraumatic-stress disorder • Psychopathology • Psychiatric diagnosis • Terrorism • DSM-5

LEARNING OBJECTIVES: Clinicians will: (1) review the types of mental-health sequelae that can be expected in the wake of disasters, (2) differentiate between psychiatric disorders such as *posttraumatic-stress disorder* (PTSD) and *distress*, and (3) will be able to use these differentiations to direct interventions and services for disaster-affected persons.

LESSON ABSTRACT: In this lesson, the author defines three main types of disasters: *natural* (e.g., earthquakes), *technological* (e.g., accidental explosions), and *catastrophic attacks* (e.g., intentional, malevolent human activities). PTSD is typically the most common psychiatric disorder among individuals exposed to disasters. This lesson examines PTSD as a diagnosis in relation to disasters, as well as in relation to other types of post-disaster disorders, psychosocial responses, and resilience. The author notes that accurately assessing mental-health sequelae among disaster survivors is an essential starting point in responding to disasters, as it provides the foundation on which effective disaster responses for affected populations should be built. The author suggests that selecting appropriate interventions should be based on the results of complete, accurate psychiatric assessments.

COMPETENCY AREAS: This lesson addresses gaps in knowledge and understanding of mental-health sequelae of populations exposed to disasters. In particular, it guides readers in the critical differentiation of psychopathology and distress and the importance of this distinction for the effective selection of interventions specific to the needs of individuals in relation to trauma exposure and mental health response to the trauma. With information provided in this lesson, mental health professionals will be equipped to assess members of disaster-affected populations and identify interventions and treatments appropriate to identified needs of individuals.

Introduction

This lesson reviews the existing literature on mental-health outcomes due to disasters and identifies predictors of psychosocial sequelae among adults. It draws on empirical evidence gathered from a wealth of disaster research conducted over the past several decades. Lastly, this information is applied to establish a coherent framework of practical recommendations that mental health professionals can apply during disaster responses.

Disaster Typology:

Presently, three main disaster types are recognized:

1. **Natural disasters (e.g., earthquakes, floods, tornadoes, and volcanoes—these are sometimes termed, "acts of God");**
2. **Technological accidents (e.g., airplane crashes, structural collapses, and major explosions involving human error, rather than malevolent intent); and**
3. **Intentionally generated human acts of mass trauma (e.g., terrorists attacks, such as those perpetrated in the 1995 bombing of the Oklahoma City federal building and the September 11, 2001, (9/11) attacks on New York City's World Trade Center and the Pentagon in Washington, DC, and the 2013 Boston Marathon bombing).**

The utility of disaster typologies in determining the mental-health effects of catastrophic events is complicated by how, in many cases, such typologies overlap because multiple elements are contributory. For example, after the 1993 Great Midwestern Floods, when the Mississippi and Missouri rivers overflowed their banks, many affected persons blamed the Army Corps of Engineers for allowing water to wash into certain areas. Similarly, after a 1999 commercial airplane crash-landed during a severe storm in Little Rock, AR, litigants sued the airline, claiming the pilot's decision to land the airplane in such adverse weather conditions was an error in human judgment.

There has been considerable debate surrounding which disaster types are associated with the most severe mental-health outcomes. In part, this is because other characteristics of disasters that also affect outcomes are inherently linked to specific disasters, confounding efforts to disentangle causalities. These characteristics include event scope and magnitude (e.g., the number of fatalities and injuries, the geographic scale of the disaster's damage, and the amount of property destroyed); terror (encountering threats of injury or death); horror (witnessing grotesque death and destruction); and duration and repetition of the disaster trauma. Only research that separates mental-health outcomes from specific disasters' other characteristics can sufficiently address this issue, but this requires the use of consistent research methods across studies on disasters with varying characteristics, and generally, this has not been possible.

A unique dataset was generated from a series of 10 disasters of different types (natural, technological, and intentional attacks), and in it, 811 persons directly exposed to said disasters were studied by North et al.[1] This research was conducted using consistent methods, including structured, diagnostic interviews assessing all criteria for psychiatric disorders. The combined data from these disaster studies were analyzed to compare the prevalence of disaster-related PTSD across the various disasters. In this study, PTSD related to disaster exposure was most prevalent after intentional-attack disasters. However, using a multivariate model that controlled for specific disaster-related sample demographics and pre-disaster psychopathology, disaster exposures, and the numbers of disaster-related fatalities, North et al. found that the type of disaster was unconnected to PTSD when independent of other disaster-specific variables.

Terrorism involving biological and chemical agents (i.e., *bioterrorism*) is an important subset of terrorist disasters. Incidents involving bioterrorism have a number of unique features. After bioterrorist incidents, survivors might be uncertain of how severely or even *if* they were exposed to disaster-causing agents. This is possible because the effects of such agents can be delayed and direct exposure can leave no acutely observable stigmata. Disaster agents in bioterrorism can, in fact, go undetected for some time following exposure, with an emotional impact being felt only once an individual becomes aware of a potential exposure. It is difficult for individuals to assess their own risk when they do not know their status or the extent to which they were exposed to hazardous

agents. This uncertainty can produce a great deal of fear, and many people who were not exposed might believe or fear they have also been exposed. Thus, the psychiatric effects of bioterrorism can become disconnected, or *disarticulated*, from levels of exposure.[2] Large numbers of people can begin to believe they have been exposed, potentially overwhelming the healthcare systems' capacities to treat those who have actually been harmed by bioterrorist attacks.[3] The long intervals between exposure and anticipated future health effects, as with cancer and reproductive damage, can result in long-term anxiety and worry. Infectious epidemics can lead to similar uncertainties regarding exposure and to widespread anxiety and fear similar to what is observed after a bioterrorist attack.

PTSD Among Disaster Survivors

Assessing Survivors for PTSD after a Disaster:

The most studied, and usually most prevalent psychiatric disorder related to disaster exposure, is PTSD.[4] This diagnosis first appeared in the American Psychiatric Association's diagnostic nomenclature in the 1980 edition of its *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*).[5] The official introduction of this disorder into the organization's literature at this time was prompted by the need for a diagnosis that reflected the Vietnam War experience, although the syndrome had been previously described in various forms following previous wars and in relation to various catastrophes throughout history.[6]

PTSD is an unusual diagnosis because of its conditional definition, which is based on exposure to trauma.[7] This characteristic of the disorder also creates complexities for diagnosing it in both clinical and research settings. ***Trauma*** **is defined as an objective experience involving threat to life or limb.** Subjective emotional responses to trauma are not included in the definition of trauma as part of the current (*DSM-5*)[8] criteria for PTSD. **According the present definition, then, examples of occurrences that would not constitute trauma would include being fired from one's job, failing an important examination, and experiencing a large financial loss. Such events might be extremely stressful, but they are not classified as traumatic stressors because they do not constitute threats to life or limb.** Consequently, not all stressors can be classified as traumatic. This is a critical distinction because PTSD cannot be diagnosed in relation to a stressor that is not traumatic. Other diagnoses, such as *adjustment disorder*, might instead be applied in classifying posttraumatic syndromes occurring under such circumstances.

It is not enough for a trauma to have occurred for PTSD to be diagnosed. There must also be personally sufficient exposure to the traumatic event in question. For example, if a traumatic event occurs in China, the population of Brazil would not be considered exposed, and therefore, Brazilians could not be diagnosed with PTSD related to this event. **According to *DSM-5* criteria, there are three main types of qualifying exposures: (1) personal endangerment through direct exposure to a traumatic event; (2) on-the-scene eye-witnessing of others exposed to trauma who may have gruesome and horrific injuries or be killed; and (3) learning of a loved one's direct exposure to a traumatic event. *DSM-5* has clarified that witnessing media reports of the disaster ordinarily does not qualify as personal exposure**—which requires physical presence at the site of the disaster. New criteria in the latest edition of the *DSM-5*[8] has, however, added the possibility that professionals, such as emergency responders and police, can experience qualifying exposures through repeated or extreme exposures to aversive details of a traumatic event. There is not yet sufficient empirical evidence concerning this type of exposure to judge whether it is consistent with other examples of posttraumatic syndrome observed after other trauma exposures. Additionally, more research is needed to determine if the posttraumatic syndromes that develop in relation to other types of qualifying exposures described in the criteria are similar to each another or if they have very different characteristics and prevalences.

In the past, the definition of *disaster-affected populations* has included more persons than those directly exposed to trauma, with diminishing ripple effects occurring with increasing distance from the disaster's epicenter, in a concentric-circle model.[9] The concentric disaster model, however, is not well suited to conceptualizing PTSD occurrences in spatial relation to a disaster because of PTSD's conditional nature. These issues were brought into focus by the complexities of studying PTSD after the 9/11 attacks, which were massive in scope and

magnitude and affected large populations. For example, we might ask how close one had to be to the immediate danger zone of these attacks to qualify as *endangered*, *directly exposed*, or a *witness*? A study by North et al.[10] of 379 employees of companies affected by the 9/11 attacks on New York City's World Trade Center found that most of the qualifying direct exposures to trauma from the event largely occurred within one city block of where the attack took place, and all qualifying exposures took place within .75 miles of the disaster's epicenter. Yet a small number of people outside this perimeter had no known exposure to the 9/11 attacks but reported a sufficient number of 9/11-related PTSD symptoms to meet the disorder's symptom criteria. *(Granted, these individuals had very high pre-existing prevalences of psychopathology, and this likely contributed to the post-9/11 symptoms they reported.)*

Some disasters present with gradually reduced trauma intensity across radii from disaster epicenters, such as with earthquakes. In these disasters, the prevalence of PTSD might be expected to decrease as concentric distance from the epicenter increases because fewer people at greater distances would have qualifying exposures to the disaster trauma. Even with these kinds of disasters, though, trauma exposure is unlikely to align perfectly with distance from an epicenter because irregular occurrences, such as the collapse of large, unstable structures, could accentuate trauma exposures in circumscribed areas at varying distances.

Still, assessing PTSD in people who are not exposed to trauma is much like attempting to divide a number by zero: it can't, by definition, be done. And yet, many studies have examined PTSD in populations without qualifying trauma exposures. Such studies can have the unintended consequence of underestimating PTSD prevalence and its sufferers' experiences because populations with few exposures naturally report few symptoms of the disorder. Moreover, attempting to measure PTSD in populations without trauma exposures can overestimate by several orders of magnitude the expected numbers of PTSD cases after very large catastrophes. This was illustrated by a 10-fold overestimate of anticipated PTSD cases in the New York City area following the 9/11 attacks because PTSD was assumed to be present, at a diminishing rate, in concentric distances from the disaster's epicenter, in areas far beyond the perimeters of the attack's danger zone. The problem of overestimating the number of PTSD sufferers is also evident in the estimated 4% rate of 9/11-related PTSD in the largely unexposed U.S. population;[11] even this small fraction of the population would equate to 11 million anticipated cases, a potentially massive burden on treatment services if these numbers had actually materialized. As illogical as the assessment of PTSD in trauma-unexposed populations is the assessment of posttraumatic stress symptoms in trauma-unexposed populations. With no trauma exposure to anchor them, symptoms cannot be considered representative of posttraumatic-stress symptoms. It is likely, then, that symptoms measured in this way represent symptoms of other disorders, distress, or continuations of pre-existing conditions.

Assuming, however, that sufficient exposure to a qualifying traumatic event has occurred, posttraumatic-stress symptoms can be assessed in relation to the event. By definition, these symptoms must be contextually associated with the traumatic event and must begin or worsen following the event. Thus, for example, someone who has experienced life-long sleep difficulties and continues to experience the same difficulties following a traumatic event would not be classified as suffering from trauma-related sleep disturbances. A common error made when assessing PTSD—particularly in recent years as researchers have faced decreasing resources for assessing psychopathology in both research studies and clinical applications, coupled with a growing desire to study larger, more generalizable samples—is to use symptom-screening tools. These tools typically merely count symptoms following traumatic events, without determining these symptoms' temporal relationships to said events. Thus, such practices neglect to anchor symptoms to traumatic exposures. Even if symptom measures do ask about symptoms "in relation to" traumatic events, this is insufficient because whether the event qualifies as trauma and whether the individual experienced a qualifying exposure should still be established.

According to the *DSM-5*'s criteria for PTSD, the disorder's 20 symptoms (see Table 1) are grouped as follows: (1) intrusive recollection involving symptoms such as flashbacks, nightmares, and unwanted, vivid images of the event (at least one symptom required);

(2) avoidance of reminders of the event in individuals who are so overwhelmed by the experience that they avoid anything that reminds them of it (at least one symptom required); (3) negative alterations in cognition and mood related to the event, including unrealistic cognition concerning the event, negative beliefs regarding its ramifications, persistent negative emotions, and loss of interest in and detachment from others (at least two symptoms required); and (4) hyperarousal symptoms, such as excessive vigilance of further danger, being "keyed-up" and "on-edge," and difficulties sleeping and concentrating (at least two symptoms required). To meet these diagnostic criteria the prospective PTSD sufferer must persistently exhibit these symptoms for longer than one month and experience clinically significant distress or functional impairment. Moreover, the patient's symptoms must not be attributable to other medical or physiological causes.

Table 1:
PTSD Symptoms

Re-experiencing	Avoidance	Negative Cognitions/Mood	Hyperarousal
Intrusive Memories	Avoids Memories/ Thoughts/ Feelings	Event Amnesia	Irritability/Anger
Nightmares	Avoids External Reminders	Negative Beliefs of Self/Others/ World	Reckless/Self- destructive
Flashbacks		Distorted Event Cognitions	Hypervigilance
Upset by Reminders		Persistent Negative Emotions	Exaggerated Startle Response
Physiologic Reactivity		Loss of Interest in Activities	Concentration Problems
		Detachment from Others	Sleep Disturbance
		Lack of Positive Emotions	

Disaster-related PTSD Incidence and Course:

The occurrence of PTSD varies considerably after different types of disasters, as reported by many different studies. Inconsistent prevalences across disaster studies might be due to population differences, various disasters' differential mental-health effects, and inconsistencies among the research methods used to study disasters' effects.

The prevalence of disaster-related PTSD, based North et al.'s full diagnostic assessments of 811 subjects affected by 10 disasters,[1] ranged from none to about one-third, and the overall mean incidence was 16%. In this study, the highest prevalence of disaster-related PTSD was about one-third: 35% among those who exposed to a plane crash into a hotel; 34% among those directly exposed to the Oklahoma City bombing; and 35% among those in the World Trade Center during the 9/11 attacks.[1, 10] These figures suggest a general threshold of maximal PTSD prevalence for disaster studies using similar methods.

In contrast, a recent review[12] concluded that the average PTSD prevalence among directly exposed disaster survivors is about 30%–40%. This considerably higher estimate might be inflated because its symptom-screening tools did not fully assess the recognized diagnostic criteria, in efforts to mitigate, the assessment burden in its very large population sample. Inflated diagnostic prevalence is a well-recognized limitation for symptom-screening tools.[13]

The course of PTSD described in disaster studies has varied considerably. Contributors to inconsistent findings about the course of PTSD include population differences, various disasters' differential mental-health

effects, and most importantly, inconsistencies among the many research methods used to study disasters. In particular, definitions of PTSD's *onset* and *remission* have varied wildly across disaster studies. Symptom-based definitions state that PTSD's onset and remission occur when symptoms start or end. In contrast, diagnostic, threshold-based definitions define onset and remission based on the time marking the start or end of the period in which full criteria for PTSD or lack thereof are met.[14] Studies assessing PTSD using full diagnostic-assessment methods have historically defined onset and remission based on symptom-based definitions by establishing lifetime diagnoses, then identifying onset and remission based on reported times for the earliest and latest symptoms. In contrast, studies using self-reporting-based symptom scales have generally administered their instruments twice, defining onset as the time when the diagnostic criteria were met and remission as when the diagnostic criteria were no longer met.

The application of such inconsistent definitions for onset and remission and the use of different methods in various studies have resulted in markedly different estimates of when PTSD onset begins following a trauma and disagreements over the disorder's chronicity. Reported proportions of "delayed-onset" PTSD are much higher using a threshold-based definition than in studies using a symptom-based definition.[14] PTSD remission rates have been shown to be much higher in studies using full-remission criteria (the symptom-based definition) compared with studies using partial-remission criteria (the diagnostic-threshold definition). One additional problem with many longitudinal PTSD studies, moreover, is that cases of unremitted PTSD have been compared with a mixed group of remitted PTSD along with those who did not develop PTSD. To demonstrate remission, individuals who did not develop PTSD should not be included in examination of remittent versus unremittent PTSD.

Despite these differences in existing research on PTSD, though, one thing generally agreed upon is that symptoms begin very early on, usually within the first day or days following a disaster. The very early and prevalent occurrence of posttraumatic-stress symptoms even in people who do not develop PTSD makes it very difficult to differentiate between the onset of PTSD and normative symptoms common among trauma-exposed persons. The first onset of prominent avoidance/numbing responses could perhaps help clinicians more effectively identify the onset of trauma-related psychopathology.

Of course, as the longitudinal course of PTSD among disaster survivors has been studied using both threshold- and symptom-based definitions, follow-up durations have varied across these studies. Still, one consistent finding is that considerable chronicity is evident over time, with substantial proportions of those diagnosed with PTSD remaining symptomatic or even surpassing diagnostic thresholds long after their initial diagnoses. Nor have consistent, reliable predictors of PTSD remission been found by any longitudinal disaster studies to date.[14]

North et al.[15] examined posttraumatic-stress symptoms among Oklahoma City-bombing survivors who did not develop PTSD. More than one-third of the survivors who did not develop PTSD reported one or more posttraumatic-stress symptoms seven years after the bombing. Although significantly fewer people without PTSD compared to those with PTSD reported posttraumatic stress symptoms, the presence of these symptoms suggests that many people who do not develop PTSD may also experience long-term emotional effects. Survivors without PTSD reported fewer functionality problems in the first few months following the bombing compared to than persons with PTSD; however, after seven years, most functionality difficulties had been resolved, even among those still suffering from PTSD.[15]

Lastly, disaster studies have provided little useful information on the role of treatment in recovering from and preventing disaster-related PTSD. This is because most disaster studies have utilized descriptive and observational designs. Seeking treatment is likely to be confounded by prospective patients' psychopathologies and their severities, making it impossible to identify causalities between treatment and the course of PTSD in these types of studies. Controlled, randomized intervention trials are needed to discern the role treatment plays in recovery from post-disaster PTSD, but such studies have, as yet, been difficult, if not impossible, to conduct in post-disaster environments.

Risk for Disaster-related PTSD:

The prevalence and severity of PTSD can be expected to be relatively higher following disasters in which greater numbers of people are exposed to trauma and in which

those exposed experience more severe trauma exposure. By definition, PTSD is not an expected outcome among those who are not exposed to trauma. In trauma-exposed groups, however, the severity and prevalence of PTSD is expected to be greater among those with the greatest exposure to the most severe kinds of trauma; such persons typically have experienced repeated or long-lasting traumas and might also have suffered additional disaster-related stressors, such as property loss, financial hardship, and routine disruption.

The most robust and consistent predictors of post-disaster PTSD are female gender[1, 4, 16, 17] and pre-disaster psychopathology.[1, 4, 17] In general, women have approximately twice the likelihood of developing PTSD as men,[18] and this ratio holds as true for disasters as it does in other types of trauma.[17] Preexisting psychopathology, meanwhile, approximately doubles the individual's likelihood of developing PTSD after a disaster.[1, 17] A preexisting psychiatric illness, however, is neither a necessary nor insufficient basis for PTSD after such events. Many individuals with no previous psychiatric difficulties have developed well-documented PTSD following disasters, while many with previous psychiatric illnesses do not develop PTSD afterward.[1, 17, 19]

Personality is one regularly overlooked aspect of predisposing psychopathologies. Research has shown that preexisting personality disorders are significantly associated with PTSD[4] and with approximately double other individuals' risk for PTSD following a disaster.[20] Naturally, experiencing extreme events can alter how people interact with others in a way that can mimic personality disorders in the short term, making it difficult to diagnose these disorders without existing histories. Key to determining whether an individual's behaviors are due to a preexisting personality disorder, then, is examining lifelong behavior patterns, beginning long before the disaster occurred and spanning the majority of the individual's life.

Other variables, such as advanced age, lack of education, and lower socioeconomic status have been identified as predictors of PTSD, but these factors' observed contributions to the disorder have been less uniform.[4,21] Apparent associations between these variables and psychopathology might lie in a significant number of associated variables. For example, in two studies, a lack of education was associated with PTSD only because it was characteristic of women who have a significantly higher incidence of PTSD than men.[17, 19]

Meanwhile, several retrospective studies have identified avoidance and numbing symptoms as potential markers of PTSD.[22] After the Oklahoma City bombing, survivors who exhibited avoidance and numbing behaviors (i.e., reporting three or more symptoms in this category), as per the *DSM-III-R*'s definition of PTSD, rated 94% for PTSD specificity and 100% for PTSD sensitivity.[17] In other words, 94% of those who met the defined avoidance and numbing criteria also had full PTSD. Given that the–PTSD diagnosis required fulfillment of avoidance and numbing criteria, 100% of people with PTSD should meet avoidance and numbing criteria. Moreover, in addition to predicting PTSD, the avoidance-and-numbing symptom group was also associated with preexisting psychopathology, functionality difficulties, treatment-seeking behaviors, diagnostic comorbidity, and the use of alcohol or drugs in coping with disaster. **The avoidance-and-numbing symptom criteria, then, were met by only a fraction of the sampled survivors and acted as markers of PTSD psychopathology.** Intrusion and hyperarousal behaviors, meanwhile, were exhibited by only about 80% of the sampled survivors and, in the absence of meeting avoidance and numbing criteria, were not independently associated with PTSD. These findings suggest that intrusion and hyperarousal symptoms are normative (present in most survivors), representing general distress that does not necessarily imply psychopathology, in the absence of prominent avoidance and numbing symptoms.[17]

More recently, the associations between symptom groups and PTSD have been studied prospectively over the first month following trauma exposure among patients admitted to an inpatient-trauma surgery unit for traumatic-injury treatment, most often from motor-vehicle accidents.[23] The study found that *DSM-IV* intrusion and hyperarousal symptoms began quickly and leveled out, such that most admitted individuals met these criteria within days, and that avoidance and numbing symptoms more often began later and did not reach their zeniths until roughly two weeks had passed. By the end of the first week following these patient's trauma, avoidance and numbing criteria accurately identified individuals

likely to develop PTSD at the end of the first month; by the end of two weeks, avoidance and numbing criteria further identified individuals who would not likely develop PTSD by the end of the first month.

Other Disaster-related Psychiatric Disorders

For disaster-exposed individuals who cannot be diagnosed as having PTSD but are symptomatic during the first month following a trauma, as required for making a diagnosis, a new diagnosis of acute stress disorder was added to the 1994 edition of the *DSM-IV*; this diagnosis describes a condition that can be diagnosed as early as two days following an event. Once a month has passed, however, the diagnosis of acute stress disorder either reverts to PTSD in those who are still sufficiently symptomatic or is otherwise dropped. The validity and utility of this diagnosis have not been established. Many people with this diagnosis do not go on to develop PTSD, and about half of those who develop PTSD did not start out with this diagnosis.[24]

In the North et al.[1] study of ten disaster-exposed samples, the post-disaster prevalence of any psychiatric disorder was found to range from 8%–45%, with an overall mean of 20%. The second most prevalent disaster-related diagnosis after PTSD was usually major depressive disorder,[1, 17, 25, 26] but this is also sometimes found to be the most prevalent post-disaster disorder.[16] **Panic, phobic, and generalized anxiety disorders have also been reported in connection with disasters, but in lower frequencies.[4, 17, 25] Schizophrenia and bipolar disorder are not among the disorders found to arise from disaster-related trauma.**

PTSD is a disorder that often presents with several psychiatric comorbidities, and it is easy to overlook these comorbidities after a PTSD diagnosis is established. The importance of these other disorders is twofold. First, PTSD with one or more comorbidities tends to be more severe and lead to poorer outcomes than PTSD without comorbidities.[17] Second, comorbid disorders can sometimes be of greater importance in managing a patient's psychopathology than the PTSD itself; thus, not addressing comorbidities could result in suboptimal treatment.

Substance-use Disorders:

There has been considerable controversy over whether disasters lead to increased use of alcohol and other substances and of alcohol and other substance use disorders. Part of the reason for this controversy is due to the failure to clearly differentiate the *use* of substances from substance-use *disorders*.[27] A combined dataset of 697 individuals directly exposed to 10 systematically studied disasters observed a 19% post-disaster and 25% pre-disaster prevalence of alcohol-use disorder; however, new incidence of alcohol-use disorder following the disasters was observed in only 0.3% of those sampled.[27] In one study, nearly one-fifth (19%) of men exposed to severe flooding were diagnosed with alcohol-use disorder post-disaster; however, there were no new cases of alcohol-use disorder in these men after the disaster, and the prevalence of lifetime, pre-disaster alcohol-use disorder was remarkably high (49%).[28] Likewise, another study of firefighters who served as rescue and recovery workers after the Oklahoma bombing found that approximately one-fourth met the criteria for post-disaster alcohol-use disorder diagnoses; however, almost all of these disorders were present prior to the bombing.[29]

Furthermore, both alcohol *use* and alcohol-use *disorders* in relation to disaster were studied in employees of New York City companies following the 9/11 attacks.[10] Alcohol use increased slightly (less than half a drink per day) after the disaster but returned to pre-disaster levels after three years had passed, and this is consistent with the similarly small increases in post-disaster alcohol consumption reported in other 9/11 studies.[30-32] Individuals with alcohol-use disorders exhibit greater increases in alcohol consumption on days of alcohol use compared with others in these samples,[10] and people who had worked in the towers consumed more alcohol than those who had not, but this was true both before and after the disaster.[10] In fact, those who worked in the tower offices who were directly exposed to trauma during the disaster were found to consume less alcohol overall than their counterparts who had not been directly exposed to trauma during the disaster. And very few alcohol-use disorders were found to begin following the disaster, while none were among persons with direct exposure to the disaster's trauma.

It is commonly assumed that substance use after stressful events like disasters represents a means of coping with psychological distress through "self-medication."[30, 32-36] Another potential interpretation of substance use is the well-established observation that rationalization of excessive substance use is an inherent part of the psychopathology of substance-use disorders.[37, 38] Among flood survivors, coping with the disaster through alcohol use was highly associated with alcohol-use disorders (with 77% of those with existing alcohol-use disorders but in only 7% of others).[28] Among firefighter rescue and recovery responders at the Oklahoma City bombing, alcohol use in coping with the disaster was four times as prevalent among responders with existing alcohol-use disorders (44%) than it was among colleagues who did not have existing alcohol-use disorders (11%). Others have observed that increased substance use after disasters is largely limited to individuals with pre-existing substance-abuse issues or other psychopathologies.[31, 34]

Somatization Disorder and Somatoform Symptoms:

Somatization disorder has not been observed as beginning after disasters,[39] but there is presently a lack of consensus concerning somatoform symptoms. This lack of consensus has resulted at least in part from methodological inconsistencies and inconsistent applications of definitions for somatoform symptoms (i.e., medically unexplained symptoms) versus those classified as somatic (i.e., any type of symptom, potentially including symptoms related to injuries sustained during a disaster). Further confusing what are already inconsistent findings, is a failure to differentiate between new symptoms arising after a disaster from pre-existing symptoms.[28, 39] Studies have found that the vast majority of somatoform symptoms observed after disasters were present prior to said disasters and that no substantial increase in symptoms is associated with disaster exposure.[26, 39, 40] Robins et al.,[40] for instance, found that disaster-exposed individuals have a higher prevalence of phobias, interpersonal difficulties, and health problems prior to experiencing disaster traumas, demonstrating how preexisting personal vulnerabilities can create selection biases after disaster exposures. These preexisting characteristics might increase the likelihood of reported somatoform symptoms after disasters, and such symptoms could be incorrectly attributed to individuals' experiencing disaster traumas if their pre-existing characteristics were either unknown or are not considered in interpreting studies' findings.

The brief discussions above on alcohol-use disorders and somatoform disorders following disasters illustrate the importance of pre-disaster characteristics as determinants of mental-health outcomes following disasters. Some populations have higher rates of pre-disaster vulnerabilities of considerable importance in post-disaster outcomes. For example, men living on a flood plain where land was inexpensive had a high lifetime prevalence of alcohol-use disorder before a flood disaster.[28] Thus, the high prevalence of alcohol-use disorder among flood-exposed men was more attributable to a pre-existing population characteristic than to trauma arising from said flood. Similarly, male firefighter responders to the Oklahoma City bombing had a high prevalence of pre-existing alcohol-use disorder, and this was later correctly interpreted as a characteristic of the firefighters' cohort rather than as their maladaptive reaction to trauma exposure following the bombing.[41] Similarly, a study of Hurricane Katrina evacuees presenting at a shelter mental-health clinic found that 28% exhibited severe, persistent mental illnesses including schizophrenia and bipolar disorder and that 20% exhibited substance-use disorder. All told, these percentages eclipsed the 24% of members of the sample with posttraumatic stress-related problems.[42] Overall, 40% of the patients presenting for care had pre-existing psychopathology, survivors accounted for the severe and persistent mental illnesses found among the evacuees after the hurricane. These examples illustrate that, in ascribing mental health outcomes to disaster traumas, awareness of relevant preexisting characteristics among specific populations is extremely important.

Resilience

In attempting to identify psychiatric needs and intervene after disasters, psychiatric clinicians and, indeed, public-policy makers often overlook the resilience of the human spirit and fail to recognize that most people do not become psychiatrically ill after disasters. When PTSD or other psychopathology is the focus of investigation, individuals who do not meet diagnostic criteria for a psychiatric disorder, but who are clearly distressed by the event, may be overlooked or discounted. Strong

feelings and emotional reactions are nearly universal among populations exposed to severe disasters. After the Oklahoma City bombing, for example, 96% of directly-exposed survivors, most of whom did not meet criteria for PTSD, reported having one or more posttraumatic stress symptoms.[17] The majority of these highly prevalent symptoms were intrusion and hyperarousal symptoms.[17] Most of these symptoms can be expected to generally diminish with the process of healing over time.[15]

Other findings that might also easily be neglected in considering the mental-health consequences of disasters include the occurrence of positive outcomes, benefits, and growth observed among some catastrophe survivors. Even after the most devastating of disasters, some people come through the experience unscathed or even find positive elements in their experiences they would never have encountered otherwise.[43-45] A study of three different disasters found that 35%–95% of exposed survivors reported such positive outcomes.[44]

Conclusions

Accurately assessing the mental-health sequelae of disasters is an essential starting point for responding to the needs of affected populations, as it provides the foundation for building appropriate and effective disaster services. North and Pfefferbaum's[46] framework for post-disaster mental-health interventions is conceptually parallel to established approaches to emergency and medical responses to mass-casualty incidents and consists of three main processes: (1) identifying mental-health needs and cases, (2) triaging trauma responses in the short-term and referring victims to appropriate service providers, and (3) providing appropriate mental-health interventions when necessary.

A fundamental principle underlying the conceptual basis for post-disaster mental-health responses is that appropriate assessments of post-disaster psychopathology and distress are necessary for accurate estimations of mental-health needs, as well as for delivering care suited to identified needs. Estimating the prevalence of psychopathology and selecting interventions ultimately relies on full assessment of diagnostic criteria for psychiatric disorders. Symptom-screening tools can be used to reduce the burden of such assessments by pre-identifying populations at greatest risk for trauma-related disorders, but following that, a more resource-intensive clinical evaluation to identify cases and estimate prevalence of psychopathology is essential.

Indeed, accurate assessments are critical because different types of post-disaster mental-health sequelae require different types of care. For a minority of disaster-affected persons who develop psychiatric disorders, psychotherapy (cognitive- and behavioral-based therapies and major-depressive disorders and exposure therapies for PTSD) and medications (largely antidepressants and adjunctive medications for PTSD and major-depressive disorder) are indicated. The effectiveness of these treatment modalities is well established for these disorders in general treatment settings, although less evidence for these modalities has been provided by research conducted specifically in post-disaster settings.[46]

Crucially, though, the far more prevalent, negative emotional responses and distress that occur among most people in disaster-affected communities—including those who do not develop psychiatric disorders—should not be overlooked or confused with psychopathologies emerging from disasters. Public-health interventions can be useful in addressing these aspects of disaster experiences and might include psychoeducation, psychological first aid, supportive crisis counseling, and social-services provision.[46] Although not yet tested in formal studies, these practical and intuitive interventions are based on expert consensus.

About the Faculty

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L003355

Multiple-Choice Questions

45. Which of the following is one of the most robust and reliable predictors of PTSD after a disaster?

A. Youth

B. Higher socioeconomic status

C. Ethnicity

D. Preexisting psychopathology (especially personality disorders)

46. Which posttraumatic stress-symptom type is considered a marker for PTSD psychopathology?

A. Intrusion symptoms

B. Avoidance-and-numbing symptoms

C. Negative cognitions and moods

D. Hyperarousal symptoms

47. Which of the following would be considered representative of a trauma?

A. The local economy was devastated.

B. A favorite community landmark was destroyed.

C. People had to run for their lives.

D. Many homes and businesses were badly damaged.

48. Which of the following is *not* ordinarily considered as qualifying trauma as part of the diagnostic criteria for PTSD?

A. Watching graphic TV news accounts of strangers being injured or killed in a disaster

B. Being an eyewitness to others' injuries and deaths during a disaster

C. Learning that one's spouse was physically endangered in a disaster

D. Personal physical endangerment during a disaster

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Best Practices in CME

The Mental Health Sequelae of Major Disasters

By Carol S. North, MD, MPE

ID#: L003355

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium knowledge and daily practice.

CME Lesson Overview

This lesson guides readers in the critical differentiation of psychopathology and distress and the importance of this distinction for the effective selection of interventions specific to the needs of individuals in relation to trauma exposure and mental health response to the trauma. The author notes that accurately assessing mental-health sequelae among disaster survivors is an essential starting point in responding to disasters, as it provides the foundation on which effective disaster responses for affected populations should be built.

Key Point 1: Posttraumatic Stress Disorder

PTSD is usually most prevalent psychiatric disorder observed in relation to disaster exposure. PTSD by definition requires exposure to a traumatic event. According to DSM-5 criteria, three main types of qualifying exposures include: (1) personal endangerment through direct exposure to a traumatic event; (2) on-the-scene eye-witnessing of others exposed to trauma who may have gruesome and horrific injuries or be killed; and (3) learning of a loved one's direct exposure to a traumatic event.

Key Point 2: Risks for Disaster-related PTSD

The most robust and consistent predictors of post-disaster PTSD are female gender and pre-disaster psychopathology. In general, women have approximately twice the likelihood of developing PTSD as men, and this ratio holds as true for disasters as it does in other types of trauma. Preexisting psychopathology in general approximately doubles the individual's likelihood of developing PTSD after a disaster.

Key Point 3: PTSD Incidence, Course, and Complexities

The course of PTSD described in disaster studies has varied considerably. The largest contributor to this disagreement is attributable to inconsistent definitions of onset and remission from PTSD. The occurrence of posttraumatic-stress symptoms, even in people who do not develop PTSD, makes it very difficult to differentiate between the onset of PTSD and normative symptoms common among trauma-exposed persons. The first onset of prominent avoidance/numbing responses could perhaps help clinicians more effectively identify the onset of trauma-related psychopathology.

Key Point 4: Other Disaster-related Psychiatric Disorders

PTSD is a disorder that typically presents with several psychiatric comorbidities,

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and other disorders sometimes occur in the absence of PTSD. It is easy to overlook these comorbidities in the focus on identification of PTSD. The importance of these other disorders is twofold. First, PTSD with one or more comorbidities tends to be more severe and lead to poorer outcomes than PTSD without comorbidities. Second, comorbid disorders can be of equal or greater importance in treatment than the PTSD itself; thus, not addressing other disorders could result in suboptimal treatment.

Key Point 5: Principle of Post-disaster Mental Health Response

A fundamental principle underlying the conceptual basis for post-disaster mental-health responses is that appropriate assessments of post-disaster psychopathology and distress are necessary for accurate identification of mental-health needs, as well as for delivering care suited to the needs. Estimating the prevalence of psychopathology and selecting interventions ultimately relies on full assessment of diagnostic criteria for psychiatric disorders rather than self-report symptom tools, which are not diagnostic.

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Preventing Retraumatization in Mental Health Settings of Women with Serious Mental Illnesses

Lauren Mizock, PhD

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

KEY WORDS: Women • Mental Health • Trauma • Retraumatization • Serious Mental Illness

LEARNING OBJECTIVES: Clinicians will be able to (1) identify the risks for trauma and retraumatization among women with serious mental illnesses, (2) recognize the challenges faced in detecting, assessing, and diagnosing trauma-related psychiatric conditions, (3) identify the signs and effects of retraumatization on women with serious mental illness, and (4) integrate recommendations for trauma-informed care to prevent retraumatization of women with serious mental illnesses.

LESSON ABSTRACT: This lesson provides an overview of the existing literature on trauma among women with serious mental illnesses in order to prevent retraumatization in mental-health settings. This lesson will begin by discussing the concepts of *retraumatization* and *sanctuary trauma*. Next, the risks of retraumatization for women with serious mental illnesses will be presented. Issues regarding misdiagnoses of women with serious mental illnesses will also be examined, as well as other challenges in assessing and detecting past trauma in this group. The effects and signs of retraumatization of women with serious mental illnesses will be listed to help practitioners better direct care. Recommendations for empowering and for trauma-informed clinical work will be discussed to help practitioners avoid re-traumatizing women with serious mental illnesses. The lesson will end by exploring the dangers of pressuring survivors to forgive their perpetrators and by emphasizing the added importance of therapist self-care in working with this population.

COMPETENCY AREAS: This lesson addresses a gap in learning vis-a-vis trauma-informed care for women with serious mental illnesses. Many clinicians do not understand how to adequately identify signs of trauma, prevent retraumatization, and engage women with serious mental illnesses using trauma-informed treatment methods. This lesson will provide readers a better understanding of how to recognize, detect, assess, diagnose, and treat women with serious mental illnesses in an empowering manner.

Introduction

Women with serious mental illnesses includes individuals with major mental-health problems that significantly interfere with at least two of the following types of functionality: occupational, academic, social, or daily-life. Such diagnoses are typically schizophrenia-spectrum disorders, bipolar disorder, or severe depression.

Women with serious mental illnesses often present at mental health settings to address psychological problems that have either developed from or worsened because of previous trauma. Women with serious mental illnesses are highly likely to have histories of trauma, with some statistics estimating that as many as 51%–97% have experienced physical or sexual assault.[1]

Still, some clinicians might not be equipped to provide trauma-informed treatment to women with serious mental illnesses, risking retraumatization during care. In this lesson, factors that contribute to re-traumatizing women with serious mental illnesses in mental health-services settings will be discussed. Information regarding assessments and diagnoses will also be examined. Furthermore, clinical strategies for promoting trauma-informed care will be listed to help clinicians meet the unique needs of women with serious mental illnesses who present at outpatient services.

Retraumatization

With the growing awareness of the impact trauma has on overall mental health and diagnoses, the topic of retraumatization in mental-health settings has also come to the fore. Duckwork and Follette's recent book, *Retraumatization: Assessment, Treatment, and Prevention* provides an overview of this topic from various theoretical standpoints.[2] The authors provided the following definition of retraumatization:

> *Traumatic stress reactions, responses, and symptoms that occur consequent to multiple exposures to traumatic events that are physical, psychological, or both in nature. These responses can occur in the context of repeated multiple exposures within one category of events (e.g., child sexual assault and adult sexual assault) or multiple exposures across different categories of events (e.g., childhood physical abuse and involvement in a serious motor-vehicle collision during adulthood). These multiple exposures increase the duration, frequency, and intensity of distress reactions.*[2]

Notably, Duckwork and Follette's definition draws attention to how repeat traumatic incidents can lead to retraumatization across a lifespan. The repetition of these events contributes to the recurrence of posttraumatic symptoms. After multiple traumas, posttraumatic symptoms can return with greater intensity. Additionally, this definition underscores the presence of physical somatization symptoms among retraumatized individuals, which might lead to misdiagnoses of medical or somatic disorders, obscuring a more accurate diagnosis of *posttraumatic stress disorder* (PTSD).

Ann Jennings, PhD, former director of Maine's Office of Trauma Services, has written and spoken extensively on this topic. In a 2009 presentation, she defined *retraumatization* as follows:

> *A situation, attitude, interaction, or environment that replicates the events or dynamics of the original trauma and triggers the overwhelming feelings and reactions associated with them.*[3]

Over the course of her work, Jennings has proposed that retraumatization frequently occurs in care settings when a new incident reminds a patient of her original trauma. The triggering incident might resemble the original trauma in terms of content or interpersonal dynamics. Additionally, the patient's reaction to retraumatization might be obvious or imperceptible to clinicians, and in the latter case, this is partially because the survivor is often unaware of the link between the original event and the more recent trigger. While retraumatization is often unintentional on the part of care providers, it unfortunately worsens the very symptoms from which the patient suffers.

Often, retraumatization occurs within an inpatient unit or other residential-treatment facility. People with serious mental illnesses are likely to be hospitalized and vulnerable to force in these settings. *Sanctuary trauma* refers to violence and abuse that occurs within an inpatient unit or other residential-treatment facility. **The following definition of sanctuary trauma was adapted**

from the *Diagnostic and Statistical Manual* (DSM) description and refers to events that take place in psychiatric settings, when the patient has "experienced, witnessed, or was confronted with an event or events that threatened of involved actual death or serious injury or a threat to the physical integrity of the self or others, [such that] the person's response involved intense fear, helplessness, or horror."[4]

Individuals with serious mental illnesses have an increased incidence of trauma in general. According to one study by Mueser and colleagues,[5] 98% of individuals with serious mental illnesses reported exposure to at least one traumatic event, and 43% met criteria for PTSD due to their traumas. Another study also found high frequencies of sanctuary trauma, stating that, among subjects with serious mental illnesses, 8% had been sexually assaulted in one or more treatment facilities, 31% had been physically assaulted, and 63% had witnessed traumas.[4] These devastating rates speak to the grave risk of traumatization and retraumatization among people with serious mental illnesses in psychiatric hospitals. Moreover, the first episode of psychosis can be traumatic in itself and has been found to raise to the threshold of diagnosable PTSD.[6]

Robins et al.[7] cite William Anthony's important commentary concerning sanctuary trauma.[8] Anthony is a leader of the psychiatric-rehabilitation and -recovery movement as it pertains to individuals with serious mental illnesses, or *persons in recovery*. In this context, recovery does not signify symptom elimination, but a process by which the patient moves toward building a meaningful life consisting of self-determination, hope, and self-empowerment. Based on his vision of recovery, Anthony discusses the role sanctuary trauma plays:

> *Recovery from mental illness involves much more than recovery from the illness itself. People with mental illnesses may have to recover from the stigma they have incorporated into their very being; [and] from the iatrogenic effects of treatment settings.*[8]

Anthony sees healing patients suffering from sanctuary trauma as part of the overall recovery process. He addresses the excessive use of force and restraint in mental-health settings, saying these practices, in themselves, traumatize and retraumatize individuals with serious mental illnesses. Given the traumatizing nature of such practices, he says steps must be taken to find alternatives to these approaches, thereby reducing the use of restraints and other types of force. Unfortunately, though, sanctuary trauma continues to be a problem in many mental-health facilities, leading to compounding retraumatization.

Previous literature has shown that women with serious mental illnesses are at particular risk of trauma and retraumatization in mental-health settings. Women, in general, encounter high rates of physical and sexual violence and abuse.[9] Women who have experienced trauma are also at increased risk of developing mental-health problems.[10, 11] Moreover, traumatized women, as well as women with serious mental illnesses, are vulnerable to retraumatization.[1, 10]

Compared with their male counterparts, women with serious mental illnesses are at particular risk of experiencing sexual trauma. According to one study, 46% of chronically hospitalized women experiencing psychoses had histories of childhood incest.[12] Another study, meanwhile, shows that 55% of women receiving outpatient mental-health services reported histories of childhood sexual abuse, compared with 18% of men presenting at the same facilities.[13] A third study found 53% of women admitted to inpatient psychiatric units reported histories of physical or sexual abuse, compared with 23% of their male counterparts.[14] Clearly, trauma-informed care is needed when working with women with serious mental illnesses.

Assessment and Diagnosis to Prevent Retraumatization

Effective detection and assessment of trauma among women with serious mental illnesses is the first step to ensuring trauma-informed care for this population. Patients might be hesitant to disclose trauma histories, especially at the onset of treatment, and providers often overlook signs of trauma. One major contributing factor to retraumatization at mental-health facilities is that primary care providers, psychotherapist, psychiatrists, and other clinicians fail to inquire about or to detect signs of sexual abuse.[3] This oversight frequently leads to misdiagnoses, lack of treatment, or misguided treatment.

In some cases, the provider might fail to screen or assess persons with mental illnesses for trauma.[3] Alternatively, reports of past and current abuse might be ignored, disbelieved, discredited, or judged to be irrelevant to treatment altogether. These negative experiences with providers can add to the already fragile levels of trust that patients have for authority figures; others in caregiver roles have violated their trust in the past by exploiting them or neglecting to protect them from abuse. Whether this treatment from providers was deliberate or accidental, a patient can feel her trauma is being dismissed, and she might therefore be less likely to access care in the future.

Assessment issues in trauma-informed care for women with serious mental illnesses can also involve providers' diagnostic mislabeling. Judith Herman's classic work *Trauma and Recovery* discusses the implicit bias toward victim blaming in the mental-health field.[10] There has been a historic tendency for providers, over-focusing on their patients' psychopathologies, to seek out problems in the characters of survivors and to assume such flaws predispose their patients to abuse and violence. Herman acknowledges that psychopathology might exist prior to abuse, but she also asserts that it can result from abuse. Nevertheless, there is continued focus on women's predispositions to abuse and violence in discussions of women's traumas. Trauma survivors might present with symptoms of anxiety, depression, somatization, psychosis, or characterological issues. However, Herman argues that this symptomatology presents differently among trauma survivors.

Herman indicates that the accurate detection and diagnosis of trauma can be obscured by survivors' presenting with problems that are not clearly related to trauma, such as those related to relationships and selfhood.[10] Both parties therefore often lack awareness of the connection between such problems and trauma. Moreover, trauma survivors often have multiple diagnoses before complex PTSD is recognized. These symptoms might include somatization, represented by disruptions in trauma survivors' senses of body and pain storing. Such persons might be diagnosed with borderline-personality disorder because they lack feelings of safety in relationships, as well as un-boundaried attachments. They can also be misdiagnosed with dissociative-identity disorder due to dissociative symptoms, identity disturbances, and other effects resulting from trauma.

To capture how these symptoms cluster repeat-trauma survivors, Herman[10] proposes a new diagnosis, *complex PTSD* (C-PTSD). In summary, criteria for C-PTSD include (1) subjection to totalitarian control over a prolonged period in war, or within cults, domestic life, or childhood, and within systems of sexual exploitation; (2) alterations in affect regulation, including self-injury, suicidality, dysphoric mood, anger, and sexual compulsivity or inhibition; (3) alterations in consciousness involving symptoms such as dissociation, depersonalization, and de-realization; (4) alterations in self-perception, such as feelings of helplessness, shame, guilt, self-blame, stigma, and a feeling of being different from others, including a sense of specialness, isolation, and difficulty in being understood; (5) alterations in perceptions toward the perpetrator, including perceptions of the perpetrator as more powerful than he is in reality, preoccupations with taking revenge on the perpetrator, and rationalization of or identification with perpetrator; (6) alterations in relations with others, including withdrawal, distrust, poor self-protection, and searching for a rescuer; and, lastly, (7) alterations in systems of meaning, including loss of faith, hopelessness, and despair.

Field trials were conducted to identify clinical support for the inclusion of C-PTSD in the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders*, DSM-5. However, researchers were unable to identify empirical support for the diagnosis. Alternatively, then, some revisions were made to the criteria of PTSD to be more inclusive of Herman's proposed symptoms for C-PTSD. More research is needed to evaluate the presentation of C-PTSD and whether it indeed differs from traditional PTSD.[15]

Formal evaluation can be conducted using a number of scales assessing PTSD and retraumatization, as described in Mueser et al.,[16] *Trauma History Questionnaire* (THQ),[17] the *Clinician-Administered Posttraumatic Stress Disorder Scale* (CAPS),[18] and the *PTSD Checklist* (PCL).[19] Mueser and colleagues found these scales to be moderate to high in interrater and internal consistency reliability with a sample of individuals with serious mental illness. Fallot and Harris also developed the *Trauma-Informed Program Self-Assessment Scale*,[20] which can be used to

evaluate the effectiveness of a mental health program in reducing the risk of sanctuary trauma and providing trauma-informed services. Other scales have been developed to assess complex trauma, including the *Structured Interview of Disorders of Extreme Stress* (SIDES). [21]

Retraumatization in Mental Health Settings

Trauma survivors can often be at risk of revictimization by their caregivers, given their tendencies to engage in interactions that replicate the behaviors of those who perpetrated their original traumas.[10] This vulnerability can cause sexual abuse by care providers, abuse from peers in a treatment program, and reenactments of physical or sexual abuse-like scenarios within inpatient units. Some possible scenarios include force-feeding, restraint, and other uses of force in psychiatric hospitals.

Jennings[3] describes the experience of retraumatization in a mental-health setting. Due to replications of trauma in mental-health settings, trauma survivors feel they are unseen and unheard by their care providers. Moreover, their treatments can remind them of how they were prevented from speaking out about their abuse. Their providers can therefore make them feel blamed and shamed for their traumas—as, frequently, the perpetrators of their traumas made them feel—for not cooperating and behaving like "good patients" (or "good victims"). They can also feel controlled or made powerless by their providers. They can feel trapped in hospitals or in provider relationships in which they feel unprotected and susceptible to further abuse. They might experience violations to their privacy and boundaries, and can feel objectified and betrayed by their providers, as they were by the perpetrators of their traumas. As a result, services that should help them only succeed in mirroring their relationships with the perpetrators of their traumas.

Women with serious mental illnesses have unique situations to consider in terms of retraumatization. **Retraumatization can potentially magnify the cognitive symptoms of mental illnesses, including a sense of confusion and lack of clarity. Women with serious mental illnesses can become increasingly paranoid, anxious, and fearful when their past traumas are triggered. They can also become increasingly depressed due to the impact of such situations on mood and sense of self, leading to hopelessness and despair. It is essential that providers pay careful attention to the trauma content of delusions, as histories of abuse are often communicated through distorted thoughts about the present.** Attributing signs of abuse solely to a patient's psychosis is invalidating. Dismissing the trauma survivor's experience trauma can therefore have a retraumatizing effect in itself.

Jennings[3] indicates that people with histories of trauma who are later re-traumatized in mental-health settings tend to present with diminished trust in providers in general and might be less willing to engage in treatment. Retraumatization in mental-health settings can increase self-injurious behavior and aggravate the intrusive symptoms of trauma, including nightmares, flashbacks, and other re-experiencing symptoms. When these symptoms are extreme, they can take on delusional qualities. The intensity and chronicity of a patient's symptoms can increase, both pre- and post-discharge from inpatient and outpatient facilities. As a result, these women can be more likely to experience symptom and to require re-hospitalization. A revolving-door scenario quickly develops, such that the patient's symptoms become worsened because of retraumatization during each successive stint at mental-health facilities, yet they are repeatedly returned to these settings, risking further retraumatization.

Lenore Walker has written extensively on providing mental-health services to traumatized women. In *Abused Women and Survivor Therapy: A Practical Guide for the Psychotherapist,*[11] Walker identifies the ways abuse blocks access to help in the first place. For example, abuse can lead to a sense of denial, given that the perpetrator often silences or threatens the victim, denies the abuse is occurring, or labels the abusive experience something other than what it is. Enablers of the abuse can also silence or dismiss traumatic events.

And yet, denial can also be a protective measure taken by trauma sufferers to prevent distress and manage their conflicting views on their abuse.[11] The denial trauma survivors often engage in is self-protective, helping them to avoid addressing their traumas. But such denial can delay the treatment process until safety has been established or until a patient is ready to begin treatment herself. Denial can also be used to

avoid direct confrontation with and additional aggression from perpetrators. Lastly, denial of the abuse itself is often rooted in cultural norms, and through denying her trauma, a survivor might be seeking to avoid the potential shame such abuse would bring to herself, her family, or her community.

As a result, survivors may feel shameful, guilty, and responsible for their traumas; and these feelings can interfere with their accessing help.[11] Self-blame often occurs if the perpetrator and others tell the survivor she deserved to be abused. The perpetrator might have deflected responsibility to the survivor to maintain power, or the survivor might engage in self-blame to feel a sense of control over what has happened to her. Lastly, Western culture tends to blame victims, and self-blame might reflect an internalization of these cultural views. Victim blaming allows the public to remain passive and avoid taking action, adding to the illusion that others are immune to violence and abuse.

Violence and abuse can cause cognitive confusion and dissociative effects that interfere with memory and clarity about what happened to the survivor.[11] This, in turn, can lead to difficulty recognizing, talking about, and naming what happened. Cognitive confusion can lead to impaired concentration, dissociation, flashbacks, nightmares, and hypervigilance. Survivors might also fear losing functionality by addressing their traumas. Clinicians can reassure their patients that sustaining functionality is a primary goal of treatment.

Another issue concerning trauma that can prevent survivors from accessing help is the survivor might fear punishment from their trauma perpetrators.[11] Such retaliation can come directly from the perpetrating caretaker, partner, enabler, or other involved party. Retaliation can involve verbal punishment, scapegoating, or isolation. Alternatively, the survivor might fear isolation from her family or community as a result of exposing the abuse she has experienced to a provider.

Trauma survivors can also develop "people-pleasing behavior" as a coping mechanism learned from the abuse, such that they have been forced to appease their trauma perpetrators.[11] People-pleasing can prevent survivors from revealing their abuse and trauma, making them instead focus on being a "good patient" or "easy" for the provider to deal with. People-pleasing might have been part of how the trauma perpetrator conditioned the survivor while coercing her into cooperating with the abuse. It should also be noted that the survivor might develop people-pleasing behavior to satisfy their perpetrators' enablers, such as other family members or caregivers who permit abuse or deny its existence.

Lastly, patients might avoid mental-health treatment for their traumas for fear of provider re-victimization.[11] As discussed above, survivors are vulnerable to sexual abuse by their care providers. Moreover, survivors might fear their care providers' dismissing or denying their traumas. Walker cites the mental-health field's history of identifying survivor stories with "screen memory," delusions, and secret fantasies and with psychologists' wish attributed to Oedipal complexes to their patients. Though these ideas have not been supported by research, they very well might prevent trauma survivors from seeking help.

Clinical Recommendations

The existing literature makes a number of clinical recommendations regarding how to avoid re-traumatizing women with serious mental illnesses at mental-health facilities. Herman[10] outlines ways the relationships between patients and providers can constitute healing relationships that validate victims' experiences. For one, the clinician can avoid any actions that seem controlling; instead, he might help the patient feel empowered in managing her behavior. While patients might need to be hospitalized when their behavior becomes a significant risk to themselves or others, they should be allowed as much free choice as possible. Clinicians should also be aware that transference can occur, such that the clinician is placed on a pedestal as the patient's idealized rescuer. Conversely, the patient might project the trauma perpetrator's identity onto the therapist, as both are individuals in caregiver roles and caregivers have historically exploited the patient.

Walker[11] makes a number of other recommendations concerning survivor therapy that can help care providers avoid re-traumatizing women with serious mental illnesses. First, the provider can provide the patient with a sense of safety and of being understood, given such a patient's likely history of having her abuse denied or dismissed. Likewise, restoring clarity of judgment is

important part of the therapy process, given that perpetrators and enablers often challenge or neglect survivors' feelings about their abuse. Alternatively, the symptoms expressed by trauma survivors might include distorted thinking and confusion that can be reversed if a patient achieves greater cognitive clarity during mental health treatment. Patients might also need to be gently challenged regarding their internalized self-blame and tendencies to deem themselves responsible for their abuse.

Furthermore, clinicians can educate their patients on the effects of trauma and provide treatment that effectively reduces its symptoms.[11] Such treatment might take the form of a range of trauma-specific or more general interventions demonstrated to have benefits for trauma survivors. Providers can allow patients to pace themselves throughout their treatments and to set their own timetables for addressing their traumas, thereby giving them feelings of self-control. This approach, specifically, honors their self-protective instincts and defers to their readiness to address their traumas. Survivors might, moreover, benefit from understanding the systemic nature of oppression toward women, and toward women with serious mental illnesses especially, given their double risk of being victims of violence. Clinicians can then focus on re-empowering female survivors with strength-based approaches that instill confidence in their patients' abilities to make decisions about their lives and avoid further abuse.

Some clinicians might, meanwhile, pressure survivors into forgiving their perpetrators or those who enabled their abuse. This is because some view forgiveness as a necessary step toward healing in cases of trauma. At worst, pressuring a patient to forgive those who have harmed her can contribute to retraumatization. In the very least, pressuring a patient to forgive can seem to dismiss legitimate anger toward her trauma's perpetrator. Rushing forgiveness can challenge the patient's valuable survival reaction to avoid, condemn, and protect herself from the perpetrator.

Malcolm, DeCourville, and Belicki[22] address this issue in *Women's Reflections on the Complexities of Forgiveness*. In it, they indicate that forgiveness research often presents this construct as positive, while sexual-abuse literature is more ambivalent. One challenge is that there are variations on how *forgiveness* is defined. Ultimately, it is recommended that a survivor decides herself whether forgiveness is a goal or desired outcome of her therapy; the survivor should be allowed to decide when, if, and whom she forgives.

That said, recent research has suggested that forgiveness is not always necessary in ensuring positive outcomes for trauma therapy;[22] rather, focuses on self-repair and internal healing should take precedence during treatment. Pushing forgiveness can also interfere with achieving an adaptive form of forgiveness. Maladaptive forms of forgiveness can backfire and contribute to further self-blame, passive resignation, and a return to abusive relationships.

Clinicians' own self-care and -awareness are central to preventing the retraumatization of women with serious mental illnesses. Herman[10] indicates that trauma therapists might experience "countertransference trauma" or vicarious trauma, involving losses of faith in therapy or humanity, nightmares, distress, contagious dissociations, dysphoric moods, and other negative effects after listening to trauma survivors' stories. The clinician might also feel an excessive sense of responsibility, guilt, or incompetence when working with trauma patients. Too, providers can encounter countertransference, involving identification with the abused and feelings of intimidation or incompetence in treating a survivor. Providers might also experience "witness guilt," similar to survivor guilt, for not having gone through the abuse their patients describe. Conversely, countertransference might involve such bewildering experiences as identifying with a perpetrator or experiencing sexual arousal, which can be difficult to discuss during a supervision or consultation. **These experiences can lead to burnout and further let the patient down.**

Jennings[3] indicates that patient retraumatization has a significant impact on staff and providers. Retraumatization can lead to higher rates of staff assault and injury, less treatment compliance, and high rates of consumer complaints. Staff can face increased level of stress and secondary trauma as a result of witnessing trauma within inpatient units. Hence, higher rates of staff turnover and lower staff morale can occur. These outcomes can also be experienced by outpatient clinicians, suggesting risks for provider illness and absence. Clinicians might become disengaged in the treatment

process as well, reducing the effectiveness of their care and creating risks of retraumatization.

It is essential to maintain effective boundaries with patients suffering from trauma.[10] While, at times, traumas can lead survivors to request more flexible boundaries, giving in to too much can make patients feel unsafe. At other times, clinicians might feel victimized by their patients, who might reenact their abuse or place unrealistic expectations on their therapists. It is important to conduct formal and informal consultations with each patient at the outset of services to delineate boundaries and reaffirm commitments from both sides, thereby establishing a safe environment. Consultation, peer supervision, and other support systems are essential to conducting trauma care. As Herman states, "No one can face trauma alone."

Conclusion

In conclusion, women with serious mental illnesses are at greater risk of retraumatization, both as women and as individuals with psychiatric disabilities. These women are uniquely vulnerable to sanctuary trauma as well and might have experienced multiple traumas in mental-health settings, preventing them from accessing care. Providers should ensure their competence in treatment and communicate their experience to their patients to instill confidence and a sense of safety. Providers should also be aware of the factors that mask trauma symptoms and prevent sufferers from accessing care. An empowerment-oriented approach to all clinical work with women with serious mental illnesses should, however, ensure effective treatment and reduce the incidence of retraumatization in mental-health facilities.

About the Faculty

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Multiple-Choice Questions

49. A person's experiencing or witnessing an event that involves actual or threatened death, serious injury, or a threat to the physical integrity of self or others in a psychiatric setting, such that the individual's response involves intense fear, helplessness, or horror, is the definition of:

A. retraumatization.

B. sanctuary trauma.

C. posttraumatic mental-health care.

D. sanctuary harm.

50. Compared with their male counterparts, women with serious mental illnesses are at particular risk of:

A. sanctuary trauma.

B. sexual trauma.

C. physical abuse.

D. sanctuary harm.

51. According to this lesson, trauma survivors avoid addressing their abuse due to all of the following reasons, *except*:

A. denial.

B. fear of punishment by the perpetrator.

C. fear of therapist re-victimization.

D. depression.

52. All of the following are unique considerations concerning the retraumatization of women with serious mental illnesses, *except*:

A. Providers should avoid buying into patients' delusions.

B. Retraumatization can exacerbate mental illnesses' cognitive symptoms.

C. Retraumatization can exacerbate symptoms of paranoia and anxiety.

D. Retraumatization can exacerbate symptoms of depression and hopelessness.

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Best Practices in CME

Preventing Retraumatization in Mental Health Settings of Women with Serious Mental Illnesses

By Lauren Mizock, PhD

ID#: L003356

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium knowledge and daily practice.

CME Lesson Overview

This lesson provides an overview of the existing literature on trauma among women with serious mental illnesses in order to prevent retraumatization in mental-health settings and begins by discussing the concepts of *retraumatization* and *sanctuary trauma*. Issues regarding misdiagnoses of women with serious mental illnesses are examined, as well as other challenges in assessing and detecting past trauma in this group. Recommendations for empowering and for trauma-informed clinical work are discussed to help practitioners avoid re-traumatizing women with serious mental illnesses. The lesson concludes by exploring the dangers of pressuring survivors to forgive their perpetrators and by emphasizing the added importance of therapist self-care in working with this population.

Key Point 1: Assessment

Given the high incidence of violence and abuse experienced by women with serious mental illness, assess these women for a history of trauma, including sanctuary trauma, sexual trauma, and complex PTSD.

Key Point 2: Examine Symptoms

Examine the potential trauma content and triggers in the symptoms associated with the serious mental illness, such as depression, anxiety, dissociation, and psychosis.

Key Point 3: Identify Barriers to Help

Discuss barriers to getting help, such as: denial, self-blame, confusion, fear of punishment, people-pleasing behavior, and avoidance.

Key Point 4: Validation

Validate the experience of trauma reported by survivors with serious mental illness and gently challenge tendency to self-blame.

Key Point 5: Psychoeducation

Educate the patient on the effects of trauma and provide treatment that effectively reduces its symptoms.

Key Point 6: Exercise Caution

Avoiding pressuring the survivor into forgiving the perpetrator and encourage her to take her time to decide when, if, and whom she forgives.

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Notes

L003357

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Adjunctive Pharmacological Agents in the Treatment of Schizophrenia

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

Medications mentioned in this lesson that are not approved for schizophrenia by the FDA are as follows:

Amphetamine, aspirin, benzoate, bexarotene, biperiden, bupropion, buspirone, carbamazepine, cholecystokinin-octapeptide, citalopram, clonazepam, cyproeptadine, D-alanine, D-serine, dehydroepiandrosterone (DHEA)/testosterone, dextroamphetamine, duloxetine, famotidine, fluvoxamine, gamma endorphin, glycine, granisetron, imipramine, insulin, ketokonazole, L-theanine, L-tryptophan, lamotrigine, levamphetamine, medroxyprogenesterone, methylphenidate, metformin, mirtazapine, mianserin, MK-0777, modafini, N-acetylcysteine, nefazodone, ondasetron, oxytocin, paroxetine, pioglitazone, pramipexole, procyclidine, promethazine, propentofylline, protirelin, raloxifene, reboxetine, rimonabant, sarcosine, sildenafil, tandospirone, topiramate, trazodone, tropisetron, valproate, zonizamide.

KEY WORDS: Schizophrenia • Adjunctive • Augmentation • Drugs • Compounds

LEARNING OBJECTIVES: This lesson summarizes current and older evidence concerning the role of compounds used to enhance the efficacy and tolerability of antipsychotics in schizophrenia.

LESSON ABSTRACT: Pharmacologic treatments intended to reduce neurotransmission through the dopamine D2 receptor have been the only proven therapeutic mechanism for *schizophrenia and schizoaffective disorder* (SZ/SA). However, in light of these psychoses' multifactorial geneses and pathogeneses, it is unlikely that the available antipsychotic drugs are equally effective at suppressing every symptom of these disorders. This has prompted the use of polypharmacy strategies, including multi-target pharmacotherapy, which is treatment incorporating one or more add-on medications and supplements. Multi-target polypharmacy strategies include the off-label prescription of adjunctive agents already in use, such as antidepressants, mood stabilizers, and benzodiazepines, as well as the use of novel potentially adjunctive agents, based on several non-dopaminergic hypotheses (i.e., serotonergic, noradrenergic, glutamatergic, gamma-aminobutyric-acid related, and cholinergic-neurotransmission, neuroprotective mechanisms and brain neuroplasticity). This review presents the current state of evidence underpinning the augmentation of antipsychotics with old (antidepressants, lithium, antiepileptic agents, and benzodiazepines) and new molecules and compounds in treating sufferers of SZ/SA. The rationale for the use of these agents in augmenting antipsychotics lies in the behavior of combinations of two or more drugs or agents whose mechanisms affect the central nervous system differently, thereby enhancing overall efficacy and tolerability. However, it should be noted that, to date, no agent for enhancing the efficacies and tolerabilities of schizophrenia-combative antipsychotics has been approved by the *U.S. Food and Drug Administration* (FDA).

COMPETENCY AREAS: This lesson provides a brief overview of pharmacoepidemiological data and studies examining the efficacy of agents used as antipsychotic-adjunctive treatments to enhance therapy outcomes for patients with schizophrenia. Upon completing this lesson, readers will be able to improve their clinical practices through their familiarity with literature examining the value of drug combinations in schizophrenia treatment.

Introduction

Schizophrenia and schizoaffective disorder (SZ/SA) are pervasive and debilitating conditions. Of the two, schizophrenia has the highest disability weight,[1] and according to 2010's Global Burden of Disease Study, its burden peaks during the most productive years of human life.[2] Meanwhile, schizoaffective disorder seems to be of similar quality and nature.[3] However, the biological mechanisms underlying both disorders remain elusive, despite these conditions' clinical significance.

SZ/SA are complex disorders with symptoms comprising delusions and hallucinations (positive symptoms), avolition, anhedonia (negative symptoms), and affect disturbances including depression, aggression, and cognitive deficits. **The dopamine hypothesis is the only theoretical explanation to draw a direct connection between the appearance and treatment of symptoms.[4, 5] However, it is becoming increasingly apparent that other neurotransmitters, such as glutamate and serotonin, are also involved in these disorders' etiopathogenesis.** Given the complexity of schizophrenia's pathophysiology and expression, multifactorial approaches have been proposed for the development of new pharmacological agents. These approaches include "polypharmacy" and "intramolecular polypharmacy," in which a single drug reacts with multiple receptor types.[6] These multi-target agents, also called "multifunctional drugs,"[7] have more than one putative, therapeutic mechanism, and this approach might lead to the development of drugs for the selective treatment of SZ/SA.

International guidelines recommend antipsychotic monotherapy as the treatment of choice. However, in clinical practice, about 20% of patients receiving antipsychotics are treated with antipsychotic polypharmacy (i.e., the administration of two or more antipsychotics).[8] **There are three commonly used terms describing drug co-administration: combination, augmentation, and add-on. The term *combination* includes virtually every way two medications can be combined. *Augmentation* implies that the secondary medication provides additive effect to the primary prescription, and *add-on* refers to introducing an extant, possibly effective treatment that cannot or should not cease.[9, 10]**

Multi-targeted Treatments

The aim of augmenting antipsychotics is to combine two or more drugs or agents whose mechanisms have different effects on the central nervous system, in an attempt to enhance efficacy or tolerability. This is termed *multi-targeted treatment*, and its implementation is based on several rationales:

- **The multifactorial geneses, genetic heterogeneities, and pathogeneses of schizophrenia and other functional psychoses and disorders cannot be attributed to any single cause.[11, 12]**
- **In light of these conditions' clinical polymorphism, it is unlikely that any one antipsychotic will work equally well against positive, negative, and mood-based symptoms, as well as against cognitive and functional deficiencies and quality-of-life deficits, while also effectively preventing behavioral disturbances in all patients. Indeed, although clinical guidelines recommend the routine use of a single antipsychotic drug in a standard dosage,[13-16] high-dose and combined-antipsychotic prescriptions are common in clinical practice.[17]**
- **Collectively, SZ/SA patients' poor treatment responses are a compelling clinical problem. Not only does roughly one-third of SZ/SA patients respond poorly to traditional treatments;[18] antipsychotic monotherapy is often an inadequate means of managing particularly challenging symptoms, such as negative and cognitive disturbances, affective instability, anxiety, insomnia, and persistent aggression, as well as other functionality and quality-of-life impairments.**
- **In addition to dopaminergic dysregulation, serotonergic, noradrenergic, and glutamatergic pathways, *γ-amino-butyric acid* (GABA) and acetylcholine dysregulation have also been implicated in the pathogenesis of SZ/SA disorder.[19-24] Multiple studies have linked degenerative abnormalities in both post-mortem and brain imaging**

studies to the pathophysiology of SZ/SA.[25] Observed changes include ventricle enlargement, volumetric reduction, and atrophy or loss of neurons and glial cells in select cortical and limbic regions of the brain.[26-29]

- **Other findings suggest that schizophrenia is a neurodevelopmental disorder expressed when dopamine levels cause one to experience feelings of social adversity, in addition to affecting other facets of cognition.[30]**
- **Inducing neurotrophic effects can be considered a therapeutic strategy intended to augment proliferation, differentiation, growth, and regeneration, whereas neuroprotective effects slow or halt the progression of neuronal atrophy and cell death following the onset of the disease or of clinical decline.[31] Available data suggest that psychotropic treatment should target brain-protective mechanisms.[32, 33]**
- **The effects of antipsychotic agents might be enhanced by co-administration with antidepressants, mood stabilizers, benzodiazepines, and others compounds that act in conjunction with other, non-dopaminergic mechanisms relevant with the pathogenesis of schizophrenia.[26, 34-36] *However, it should be noted that the FDA has, as yet, not approved any agent for the augmentation of antipsychotic SZ/SA treatments.***

Based on these research results and clinical experiences, elucidating how the use of multiple psychotropic drugs, instead of only one (e.g. dopamine-affective medication alone), in conjunction might improve the performance of multiple signaling pathways, could lead to more efficient multi-target drug therapies for SZ/SA, especially in terms of suppression the cognitive impairments and negative and mood-based symptoms associated with such disorders.

Augmentation in the Real World: Pharmacoepidemiological Data

Adjunctive pharmacological agents have been extensively used to treat patients with schizophrenia. There are two types of adjunctive agents:

- **"Old" agents are those already in use and prescribed off-label; they comprise antidepressants, lithium, antiepileptic medications, and benzodiazepines.**
- **Newer molecules and compounds are those based on non-dopaminergic hypotheses presently under examination.**

Current pharmacoepidemiological data suggest there are established "augmentation" practices in "real world" schizophrenia pharmacotherapy. Pickar et al. report that 70% of a 200-subject sample of U.S. patients with schizophrenia received an antipsychotic administered alongside medication of another drug class.[37] Similarly, a study by Längle et al. shows that only 20% of SZ/SA patients in southern Germany who underwent follow-up examinations for 24 months after hospitalization were on antipsychotic monotherapy.[38] And Shinfuku et al. have found that polypharmacy occurred in 79% of patients with schizophrenia in Tokyo, Japan, as well as that the two-year rates for hypnotic, benzodiazepine-derivative anxiolytic, anticholinergic, antidepressant and mood-stabilizer usages were 56.7%, 49.7%, 38.3%, 21.3%, and 14%, respectively. Interestingly, they also show that, once they began polypharmacy regimens, patients continued on such course of treatment until their final visits in more than 70% of cases.[39]

Antidepressant Augmentation:

Using administrative data on the Mid-Atlantic region from the U.S. Department of Veterans Affairs, Himelhoch et al. retrospectively estimated the prevalence and incidence of antidepressant prescriptions. They found that, among the 2,412 veterans who received treatment for schizophrenia, 37.4% of patients also received antidepressant prescriptions.[40] Similarly, in a cohort of 214 Dutch psychotic-disorder patients treated by a mental health center in a circumscribed region of the Netherlands, antidepressants were prescribed in 40% of cases, and the majority (83%) of those to whom these

medications were prescribed continued taking antidepressants after one year.[41]

Mood-stabilizer Augmentation:

A cross-sectional survey of inpatients ages 18-65 at St. Andrews Hospital, Northampton, UK, was conducted to determine how frequently off-label mood stabilizers were prescribed. Its results show that 30% (75) of the 249 patients queried had been prescribed one or more mood stabilizers and that 71 of the mood stabilizers prescribed were off-label.[42] Sim et al. examined the frequency of mood-stabilizer use and its clinical correlates among hospitalized patients between 2001 and 2008 in nine Asian countries (China, Hong Kong, India, Korea, Japan, Malaysia, Taiwan, Thailand, and Singapore). Their results show that, overall, mood stabilizers were administered to 20.4% (n = 1,377) of the 6,761 hospitalized schizophrenia patients surveyed and that use increased over time.[43] Similarly, Xiang et al. surveyed the use of adjunctive mood stabilizers in Asian patients ages 55 and up using a database of 1,452 patients. Moreover, according to this survey, mood stabilizers were prescribed with a frequency of 26.7% to those in the pooled sample, this having increased from 25.5% in 2001 to 27.7% in 2009. Multiple logistic regression analyses of the entire sample also revealed that patients on mood stabilizers were (1) younger and more likely (2) to be men and (3) to have *extrapyramidal side effects* (EPS) in addition to longer illness durations.[44]

Benzodiazepine Augmentation:

Clinical experience suggests that *benzodiazepines* (BZD) are broadly prescribed in psychiatry. One survey of benzodiazepine prescriptions at a UK psychiatric hospital shows that 18.7% of inpatients received prescriptions for psychiatric indications.[45] Meanwhile, in a multicenter, pooled Asian survey by Xiang et al., the rate of benzodiazepine use was 20.7% with this trend increasing over time. The authors report that, compared with schizophrenia patients in China, Korean and Singaporean schizophrenia patients are more likely to receive BZD.[44]

All told, the above data indicate that a substantial number of SZ/SA patients do not achieve acceptable response levels with antipsychotic monotherapy, or antipsychotic therapy alone, and that this commonly leads clinical psychiatrists to prescribe augmenting agents. Differences in the use of adjunctive medications might be the result of true differences in the frequency of ancillary symptom complexes. However, among patients with ancillary schizophrenia symptoms, the prescription of adjunctive agents could be associated with other factors, such as race. For instance, among patients with recognized ancillary symptom complexes, African-American patients might be less likely than Caucasians to receive treatment. In some areas, this could be due to differences among racial groups in terms of mental-healthcare accessibility, physician perceptions, and patient beliefs and preferences.[46] Further research is needed to determine if there exist underlying biases and behaviors that affect the use of adjunctive medications among patients with schizophrenia.

Using Adjunctive Agents to Augment Efficacy and Alleviate Side Effects of Antipsychotics in Patients with Schizophrenia

This section presents an overview of the existing literature, but for the sake of brevity, it only includes data that agree with both current meta-analyses and individual randomized studies. The findings of said meta-analyses are emphasized. **It should be noted as well that none of the following adjunctive agents has been approved by the FDA for use in either augmenting the efficacy of antipsychotics or alleviating antipsychotic-induced side effects:**

Antibiotics:

A recent meta-analysis shows that introducing minocycline to antipsychotic treatment could lead to a reduction in extrapyramidal symptoms.[47] Similarly, recent randomized trials have suggested that minocycline lessens cognitive symptoms[48, 49] and improves overall functionality.[48] In fact, one randomized trial has found that ketokonazole, an antifungal medication with anti-glucocorticoid properties, is associated with reduced depressive symptoms.[50]

Anticholinergic Agents:

Two randomized studies have revealed anticholinergic agents negatively affect cognitive performance and positive symptoms (biperiden[51] and procyclidine,[52] respectively). However, the usefulness of these two anticholinergic agents for extrapyramidal symptoms is presently supported by the results of three randomized studies.[51-53]

Anticonvulsants:

A recent meta-analysis examining the role of carbamazepine in schizophrenia found that carbamazepine is a superior medication overall, but that it likely worsened positive symptoms among schizophrenia patients.[54] And yet, three other meta-analyses—two of whose samples included clozapine-resistant patients—have found that lamotrigine performed better than placebo against schizophrenia symptoms overall.[55-57] According to one of these meta-analyses, moreover, the addition of topiramate to antipsychotics regimens seemed to help treatment-resistant patients in terms of positive-symptom reduction.[56] Meanwhile, the results of another meta-analysis show that adjunctive valproate is effective against schizophrenic aggression,[58] yet this study nevertheless failed to support its use in combatting other symptoms. Similarly, one randomized study thus far has found that zonizamide can attenuate weight gain, thereby possibly augmenting the efficacy of antipsychotics in reducing symptoms.[59]

Antidepressants:

Depressive symptoms in schizophrenic patients can occur as secondary or negative symptoms,[60] as side effects of medications, as neuroleptic-induced movement disorders,[61] or as core components in various stages of SZ/SA.[62] One meta-analysis has shown that antidepressants, as a class, have beneficial effects on negative schizophrenia symptoms.[63] Likewise, similar favorable effects on positive symptoms and cognitive functioning have been shown for α2-antagonists.[64] Citalopram has proved effective at lessening schizophrenia symptoms overall according to one meta-analysis involving patients receiving clozapine treatment.[56] It has also proved effective in curbing aggressive behavior according to one randomized study.[65]

Another meta-analysis, meanwhile, has demonstrated that administering fluvoxamine reduced symptom prevalence overall,[66] and two randomized trials have shown that it provides valuable relief for those suffering from obsessive-compulsive symptoms[67] and weight and metabolic disturbances.[68] Paroxetine and trazodone have been shown to suppress negative symptoms according to one recent meta-analysis,[69] while another has found that norepinephrine and other specific serotonergic antidepressants (mirtazapine and mianserin) decrease overall and negative symptoms, respectively.[70] Furthermore, one randomized study suggests that mianserin enhances cognition in patients,[71] while another reveals that the addition of mirtazapine to risperidone could cause weight gain.[72] The combination of bupropion and cognitive-behavioral therapy was found to be effective against depressive and overall symptoms in one randomized trial examining smoking cessation in patients with schizophrenia.[73] Several other randomized trials have revealed that duloxetine is useful in suppressing negative, depressive, and overall symptoms,[74] imipramine can be used to combat overall symptoms,[75, 76] nefazodone is useful in fighting neuroleptic-induced extrapyramidal symptoms,[77] reboxetine alone and in combination with betahistine can be used to counteract weight gain,[78, 79] and trazodone can be used to suppress acute akathisia.[80]

Table 1:
Adjunctive Agents

Medications	Trade Name (US)
Antibiotics	
Minocycline	Minocin, Dynacin
Ketokonazolee	Xolegel, Nizoral
Antiholinergic Agents	
Biperiden	Akineton
Procyclidine	-
Anticonvulsant Agents	
Carbamazepine	Carbatrol, Epitol
Lamotrigine	Lamictal
Topiramate	Topamax, Trokendi XR
Valproate	Prosom, Depakote
Zonizamide	Zonegran
Antidepressants	
Citalopram	Celexa
Fluvoxamine	Luvox
Paroxetine	Paxil, Pexeva
Trazodone	Desyrel, Oleptro
Mianserin	-
Bupropion	Wellbutrin, Zyban
Duloxetine	Cymbalta
Imipramine	Tofranil
Nefazodone	Serzone
Reboxetine	Edronax

Table 1 (cont.):
Adjunctive Agents

Medications	Trade Name (US)
Antihistamines	
Famotidine	Pepcid, Fluxid
Promethazine	Phenadoz
Benzodiazepines	
Clonazepam	Klonopin
Cannabinoid Ligands	
Rimonabant	-
Trazodone	Oleptro
Glutamatergic Agents	
D-alanine	-
D-serine	-
N-acetylcysteine	Mucomyst, Acetadote
Bupropion	Wellbutrin, Zyban
Sarcosine	-
Glycine	Aminoacetic acid
Hormones	
Raloxifene	Evista
Medroxyprogesterone	Depo-Provera, Provera
Cholecystokinin-octapeptide	-
Dehydroepiandrosterone (DHEA)/testosterone	-
Oxytocin	Pitocin
Thyroid-releasing hormone protirelin	Protirelin

Antihistamines:

The results of a recent meta-analysis shows that histamine-2-class receptor antagonists are related to worsening depressive symptoms.[81] The same meta-analysis shows that famotidine is helpful in suppressing overall symptoms, while another meta-analysis suggests that promethazine decreases aggression when taken with haloperidol.[82]

Benzodiazepines:

Clonazepam was found to combat acute akathisia in one randomized, controlled study.[83]

Cannabinoid Ligands:

The intravenous administration of delta-9-tetrahydrocannabinol is associated with worsening positive, negative and extrapyramidal symptoms, as well as with decreased cognition, in schizophrenia.[84] Additionally, the cannabinoid antagonist rimonabant has been shown to be beneficial in suppressing anxiety and depressive and overall symptoms and in decreasing aggression in overweight patients with schizophrenia.[85]

Glutamatergic Agents:

One meta-analysis has shown that AMPAkines provide relief from negative symptoms in schizophrenia patients who do not respond to clozapine.[56] Similarly, glutamate agonists were associated with fewer positive and overall symptoms in a meta-analysis investigating the effects of adjunctive agents on cognitive deficits in schizophrenia.[86] D-alanine, D-serine, sarcosine, and N-acetylcysteine have also been shown to be effective against negative and overall symptoms.[87] This effect for N-acetylcysteine has also been confirmed by another meta-analysis.[88] Interestingly, a randomized trial has revealed that sarcosine could improve functionality.[89] Similarly, the co-administration of glycine with antipsychotics has been shown to diminish overall symptoms in schizophrenia, as evinced by two meta-analyses.[87, 90]

Hormones:

One meta-analysis has found that estrogen causes a decrease in negative symptoms,[91] while two randomized studies have reported that the estrogen receptor-modulator raloxifene and a combination therapy consisting of estrogen and medroxyprogenesterone enhance cognition in female patients.[92, 93] Adding cholecystokinin-octapeptide also leads to improvements in positive and overall symptoms, and davunetide has been shown to improve functionality.[94, 95] One meta-analysis reveals that the addition of dehydroepiandrosterone (DHEA)/testosterone is effective against negative and extrapyramidal symptoms.[96] Moreover, according to a recent" meta-analysis, oxytocin suppresses positive, negative, and overall symptoms.[97] One randomized study has also found that thyroid-releasing hormone protirelin attenuated negative and overall symptoms.[98]

Non-steroidal Anti-inflammatory Agents:

The results of two recent meta-analyses suggest that non-steroidal, anti-inflammatory agents reduced negative symptoms among patients with schizophrenia;[99, 100] **aspirin is effective at reducing overall symptoms according to a recently updated meta-analysis,[88]** while

one randomized study has shown that it can also suppress positive and overall schizophrenia symptoms.[101]

Serotonergic Agents:

Several meta-analyses have found 5-HT1A agonists[86] and 5-HT1A partial agonists[102] are useful in combatting positive and overall" schizophrenia symptoms, respectively. Buspirone has also been shown to have beneficial effects on both domains,[102] while the use of 5-HT3 antagonists has led to improvements in overall and negative symptoms. Specifically, granisetron use has been shown to cause marked improvements in overall and negative symptoms, whereas ondasetron has been shown to suppress negative symptoms.[103] Similarly, randomized trials have revealed that L-tryptophan has beneficial effects on memory[104] and that tandospirone,[105] ondasetron,[106] and tropisetron[107] improve cognition. Meanwhile, haloperidol augmented with cyproeptadine has been shown to reduce extrapyramidal symptoms.[108]

Stimulants:

Randomized studies reveal amphetamine,[109] dextroamphetamine, levamphetamine,[110] and methylphenidate[110-112] detrimentally affect positive symptoms, though amphetamine alone seems to enhance cognition.[113, 114] Interestingly, modafinil was associated with improved social cognition during the first psychotic episode.[115]

Other Medications:

The antigluco-corticoid ketokonazole has been associated with decreased depressive symptoms in one randomized study.[50] In another randomized study, the retinoid agonist bexarotene is associated with relief from positive symptoms.[116] Yet another randomized study finds that the dopaminergic agonist pramipexole augments antipsychotic responses for positive, negative, and overall symptoms,[117] and GABA agonist MK-0777 has been shown to enhance cognition.[118] Meanwhile, norepinephrine inhibitors have been associated with weight-loss and benefits to metabolic syndromes,[119] and one meta-analysis on phosphodiesterase inhibitors suggests that this class of agents is corrective for sexual dysfunction due to antipsychotic use.[120]

Notably, sildenafil has been found to suppress schizophrenia symptoms overall when combined with risperidone.[121] Likewise, another meta-analysis suggests that adding purinergic modulators decreases positive and overall symptoms, a finding consistent with the adenosine-schizophrenia hypothesis. The same meta-analysis also shows that purinergic modulator propentofylline reduces positive, negative, and overall symptoms,[122] and yet another meta-analysis suggests that metformin has favorable effects on metabolic abnormalities.[123] Randomized studies reveal similar effects for metformin combined with pioglitazone[124] and lifestyle interventions,[125] and pioglitazone has also been shown to reduce depressive symptoms.[124] Still another randomized study suggests that D-aminoacid-oxidase inhibitor

Table I (cont.):
Adjunctive Agents

Medications	Trade Name (US)
Non-steroidal Anti-inflammatory Agents	
Aspirin	Ecotrin, Excedrin
Serotnergic Agents	
Buspirone	BuSpar
Granisetron	Granisol, Sancuso
Ondansetron	Zofran, Zuplenz
L-tryptophan	Melatonin
Tandospirone	-
Tropisetron	-
Cyproheptadine	Periactin, Peritol
Stimulants	
Amphetamine	-
Dextroamphetamine	ProCentra, Dexedrine
Levamphetamine	Adderall
Methylphenidate	Daytrana, Concerta,
Modafinil	Provigil
Other Medications	
Ketokonazole	Xolegel, Extina
Bexarotene	Targretin
Pramipexole	Mirapex
MK-0777	-
Sildenafil	Viagra, Revatio
Propentofylline	-
Metformin	Fortamet, Glucophage
Pioglitazone	Actos
Benzoate	-
Gamma endorphin	-
Insulin	-
L-theanine	-

benzoate is helpful in reducing positive, negative, and overall symptoms,[126] while another randomized study has reported that intramuscular gamma endorphin acutely reduces positive symptoms.[127] Interestingly, in one meta-analysis that examines the effects of drugs in tardive dyskinesia, it has been found that insulin co-administered antipsychotics reduces tardive dyskinesia.[128] Finally, the addition of L-theanine to antipsychotic treatments has been shown to have enhanced effects on positive symptoms and anxiety.[129]

Conclusion

The development of new antipsychotic drugs over the past decade has not dramatically changed how schizophrenia is treated. Consequently, novel receptors are now being targeted to develop third-generation antipsychotic agents.[130-132] Other less-traditional pathways are also being examined, leading to the production of several agents presently in the earliest stages of development, including those that act on sigma receptors, cholecystokinin antagonists, neurotensin agonists, neurokinin-receptor antagonists, GABAergic enhancers, and cannabinoid receptor modulators.[133]

And yet, despite the wide array of different drug classes used to treat SZ/SA, drug resistance, partial responses, and relapse are common. It is therefore unsurprising that, at many clinical practices today, non-dopaminergic drugs are prescribed to enhance the therapeutic effects of other medications. Although none of the aforementioned agents has been approved by the FDA for use in mitigating the side effects of or augmenting antipsychotics, there are quite a few agents that can serve to lessen or altogether nullify traditional SZ/SA medications' side effects, and each there are, presently, varying degrees of evidence regarding these supplemental medications' efficacies and tolerabilities. Augmentation, meanwhile, is generally considered the best option if a primary medication provides only partial relief from symptoms. The rationale for any augmentation strategy is that the psychiatrist is simultaneously seeking to manipulate different brain functions using pharmacological agents, in the hope of providing overall symptom relief. And it is becoming increasingly evident that various non-dopaminergic receptors play an important role in schizophrenia's clinical profile. Specifically, noradrenergic, glutamatergic, and serotonergic receptors have been shown to contribute to the pathogenesis of schizophrenia's positive and negative symptoms.

The adjunctive agents employed in the various SZ/SA clinical trials mentioned above include antidepressants, lithium, antiepileptics, hormones, stimulants, and others. That said, although an ever-increasing number of augmentation trials are being undertaken, some studies have had conflicting results, and the recommendations made herein are therefore based on theoretical assumptions, rather than on evidence-based fact. Of course, as all clinicians should bear in mind, the disadvantages of an augmentation strategy include increased costs for additional treatments and (in cases of drug augmentation) increased likelihood of side effects, negative drug interactions, and a general lack of evidence that such treatments are indeed effective.

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Acknowledgements

We wish to thank Ms. Rena Kurs, B.A. (Shaar-Menashe Mental Health Center, Hadera, Israel) for her assistance in editing the present lesson.

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Multiple-Choice Questions

53. Which of the following statements concerning schizophrenia's etiopathogenesis is true?

A. The dopamine hypothesis still remains prevalent.

B. The etiopathogenesis of schizophrenia is likely to involve only one neurotransmitter system.

C. There is no evidence to suggest that the glutamatergic system is implicated in schizophrenia.

D. The dopaminergic system is probably involved in schizophrenia's etiopathogenesis but not in the treatment of its symptoms.

54. Antipsychotic monotherapy:

A. is usually prescribed in schizoaffective disorder but not in schizophrenia.

B. is the only established practice in "real world" treatments of patients with schizophrenia.

C. usually follows an antipsychotic, polypharmacy-regime trial.

D. and antipsychotic therapy alone are not always associated with acceptable levels of" treatment response in schizophrenia.

55. What is the efficacy of adjunctive antidepressants as a class in schizophrenia?

A. They definitely suppress positive symptoms.

B. One meta-analysis suggests they might combat negative symptoms.

C. They reverse cognitive deficits.

D. They reduce the extrapyramidal side effects of antipsychotics.

56. The use of aspirin as an add-on treatment in schizophrenia:

A. has been shown to reduce overall symptoms, according to a recent meta-analysis.

B. enhances cognition.

C. is associated with diminished depressive symptoms in one randomized study.

D. reduces the extrapyramidal side-effects of antipsychotics.

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Best Practices in CME

Adjunctive Pharmacological Agents in the Treatment of Schizophrenia

By Dimitrios Kontis, MD, PhD; Eirini Theochari, MD; and Michael S. Ritsner, MD

ID#: L003357

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium knowledge and daily practice.

CME Lesson Overview

The use of older and newer adjunctive agents alongside antipsychotics as part of ongoing treatment for schizophrenia has been shown to increase therapeutic efficacy and alleviate certain antipsychotic-induced side effects. Pharmacoepidemiological studies suggest combinations of antipsychotics and other psychotropic drugs are common among schizophrenia patients. Efficacy and tolerability studies on adjunctive agents have produced promising results, but to date, no such agent has been approved for enhancing the efficacy or tolerability of antipsychotics used to treat schizophrenia.

Key Point 1: Background

Given schizophrenia's multifactorial pathogenesis, it is unlikely that a single antipsychotic drug can treat every symptom of the disorder.

Key Point 2: Augmenting Antipsychotics in the "Real World"

In current clinical practices pertaining to schizophrenia and schizoaffective disorder, typical and atypical antipsychotics are frequently combined with other drugs, including antidepressants, mood stabilizers and benzodiazepines.

Key Point 3: Adjunctive Treatments and their Efficacy

Meta-analyses and randomized clinical trials of using adjunctive agents in addition to antipsychotics have shown that older and newer molecules and compounds can suppress positive, negative, depressive, and overall symptoms and help lessen aggression and improve cognitive dysfunction among patients.

Key Point 4: Adjunctive Treatments and the Tolerability of Antipsychotics

Clinical trials have shown that add-on agents can effectively decrease antipsychotic-induced metabolic abnormalities, such as sexual and extrapyramidal symptoms, in patients with schizophrenia.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Psychiatric Disorders and Psychotropic Treatment in the Postpartum Period

Asim A. Shah, MD; Awais Aftab, MD; and Samantha Latorre, MD

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

KEYWORDS: Postpartum Depression • Postpartum Psychosis • Psychotropics • Lactation • Pharmacokinetics

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) understand the prevalence and risk factors of psychiatric disorders in the postpartum period, (2) consider the negative effects of psychiatric illness on mothers and infants, (3) recall the recent implementation of the *U.S. Food and Drug Administration* (FDA) *pregnancy and lactation labeling rule* (PLLR), (4) recognize the general principles of psychotropic use during lactation, and (5) review literature on the safety of psychotropic use during lactation.

LESSON ABSTRACT: The prevalence of psychiatric disorders during the postpartum period is at least comparable to that of the general population, with some indication that the first five weeks after childbirth are a vulnerable period for the onset of psychiatric illness. Additionally, there are significant detrimental effects of psychiatric illness on the mother and infant and of factors specific to the postpartum period that influence management. All psychotropic medications are secreted in breast milk, but the majority are present only in low concentrations and can be used safely in lactating mothers. Psychiatrists are often hesitant to prescribe psychotropics to lactating mothers. In this continuing medical education lesson, we will review the prevalence and risk factors of psychiatric disorders in the postpartum period, the adverse effects of psychiatric illness on mothers and infants, the recent implementation of the FDA's PLLR, the general principles of psychotropic use during lactation, and the safety of psychotropic use during lactation, with an emphasis on the medications that are associated with significant side effects.

COMPETENCY AREAS: This lesson addresses the gaps in learning in the area of knowledge and patient care with regard to the special patient population of postpartum and lactating women. Many psychiatrists lack knowledge and an appreciation of the burden of psychiatric illness in the postpartum period, the risks of untreated psychiatric illness for mothers and infants, and how to safely prescribe psychotropic medications to a lactating mother. After reading this lesson, readers will have a better understanding of the prevalence of psychiatric disorders in postpartum mothers, the negative effects of psychiatric illness on mothers and infants, and safety concerns regarding the use of psychotropic medication during lactation.

Psychiatric Disorders in the Postpartum Period

The presence of various psychiatric disorders in the postpartum period has been recognized for centuries. Evidence strongly indicates that the prevalence of psychiatric disorders during pregnancy and the postpartum period is at least comparable to that in the general population and that pregnancy and the postpartum state are not protective against the emergence or recurrence of psychiatric illness. Additionally, there are significant, detrimental effects of psychiatric illness on the mother and infant. 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.[1] In a 2013 meta-analytic review, it was found that overall, depressed mothers provide less responsive caregiving; are more likely to discontinue breastfeeding early or have problems breastfeeding; are less likely to comply with recommended safety practices, such as the use of car seats; and their children have lower rates of preventive healthcare utilization and vaccination.[2] These significant consequences of peripartum mental illness indicate a need for practitioners to know the risks of developing these disorders to properly counsel their patients.

Postpartum Blues:

Postpartum blues, often called "baby blues," is typically defined as a transient state of heightened emotional reactivity.[3] Women most often report mild symptoms of depression, insomnia, and decreased concentration. Depressive symptoms at this time can include irritability, anxiety, and tearfulness.[4] In 40%–80% of women, symptoms of postpartum blues develop in two to three days after delivery and usually resolve within two weeks.[5] Among women who experience postpartum blues, 20% will go on to experience a major depressive episode in the first postnatal year.[3]

Postpartum Depression:

Approximately 50% of major depressive episodes presenting in the postpartum period actually have onset prior to delivery, and they are best referred to as peripartum episodes.[6] According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), the specifier "with peripartum onset" is applied to depressive disorders when the most recent episode of depression occurs during pregnancy or in the first four weeks following delivery.[7] This same specifier is also applied to bipolar disorder and brief psychotic disorder. However, clinically and for research purposes, various cut-off marks, such as up to three months, six months, or one year following childbirth, have been utilized. Approximately 30% of women with postpartum depression still report depression beyond the first year after delivery.[8]

Some of the best data on the epidemiology of unipolar major depression during pregnancy and the postpartum period comes from a quantitative review commissioned by the Agency for Healthcare Research and Quality. In the study, Gaynes et al. reported the point prevalence of major depressive disorder at three months postpartum to be 4.7% (95% *confidence interval* [CI], 3.6–6.1), the period prevalence from birth to three months postpartum to be 7.1% (95% CI, 4.1–11.7), and the incidence from birth to three months postpartum to be 6.5% (95% CI, 4.2%–9.6%).[9] The values for depressive disorder (both major and minor depression) were considerably higher than for major depressive disorder alone at 12.9%, 19.2%, and 14.5% for point prevalence, period prevalence, and incidence, respectively.[9] The data reveals just how widely prevalent depression is in the postpartum period.

Studies reviewed by Gaynes et al. in which postnatal subjects were compared with a control group revealed similar prevalence rates of depression among women of similar ages, except for one study by Cox et al.[10] in which a threefold higher rate of the onset of depression was found within five weeks of childbirth. However, no difference was found in the six-month point and period prevalence.

Despite the similar prevalence, childbirth is associated with an increased risk of psychiatric readmission for mothers during the first postpartum month compared to non-mothers, with the highest risk at 10–19 days postpartum.[11]

There are several risk factors for postpartum depression. The greatest risk is a prior history of postpartum depression. The relapse rate is about 40% if there has been a previous episode of postpartum depression.[8] Other risk factors include domestic violence or prior abuse, negative life events, low social support, low

partner support, marital difficulties, low socioeconomic status, depression and anxiety in pregnancy, prior history of depression, neuroticism, substance abuse, increased parity, and chronic illness.[8]

Bipolar Disorder in the Postpartum Period:

Women with bipolar disorder have at least a 20% risk of experiencing a severe recurrence after childbirth, and the risk of any mood episode in the postpartum period approaches 50%.[12] A population-based cohort study conducted over 30 years showed that in the first month following birth, the risk of readmission is increased in women with a history of bipolar disorder, with a relative risk of 37%. Women who have their first psychiatric admission in the first postpartum month are more likely to be meet the criteria for bipolar disorder in the future.[11]

As there are significant concerns about some mood stabilizers with regard to teratogenicity, treatment is frequently discontinued during pregnancy. The recurrence risk of bipolar disorder during pregnancy is 2.3 times higher with the discontinuation of mood stabilizers.[13] The majority of these episodes are depressive or mixed episodes. Viguera et al. reported that with lithium discontinuation during pregnancy, rates of recurrence are similar for pregnant women during pregnancy and for non-pregnant women (the first 40 weeks after discontinuation); however, recurrences are almost threefold higher in postpartum women compared to controls during equivalent period (weeks 41–60 after lithium discontinuation).[14]

Postpartum Psychosis:

Most cases of postpartum psychosis are believed to be cases of bipolar disorder rather than a primary psychotic disorder. These episodes generally consist of psychotic mania or severe psychotic depression. The status of postpartum psychosis is subject to nosological debate, as it is a heterogenous entity encompassing psychotic mania, psychotic depression, brief psychotic disorder, and psychotic exacerbations of underlying schizophrenia or schizoaffective disorder. However, the term remains in widespread clinical use.

The actual rates of postpartum psychosis are not known, but a reported psychiatric admission rate of 1–2 per 1000 births is often used as a rough estimate for postpartum psychosis.[12] Postpartum psychosis is most common in the first two weeks following delivery, usually between the first one to three days. Sudden onset and rapid deterioration are typical features of postpartum psychosis.[12] It is important to exclude medical causes of psychosis specific to the postpartum period, such as eclampsia, delirium, thyroid disorder, and infection, because these conditions are potentially fatal if not properly diagnosed and treated.

A prior history of postpartum psychosis places women at a very high risk for developing postpartum psychosis. Risk is similarly elevated for women with bipolar disorder who have a family history of postpartum psychosis. **Primiparity is the only strongly associated obstetric risk factor for developing postpartum psychosis, which is theorized to result from medication discontinuation due to concerns about teratogenicity.[12]**

Postpartum Anxiety Disorders, Obsessive-Compulsive Disorder and Posttraumatic Stress Disorder:

There is very little information in the literature on anxiety during pregnancy and the postpartum period, with much of the literature dedicated to depression and psychosis. In published reports, the prevalence of anxiety during depression ranges from 13%–21% and 11%–17% in the postpartum period.[15]

Obsessive-compulsive disorder (OCD) during pregnancy and the postpartum period is significant as pregnancy is a known risk factor for developing OCD compared to the general population and for exacerbating existing OCD symptoms[8]. An estimated prevalence of OCD ranges from 0.3%–29% during pregnancy and from 1.7%–9.0% during the postpartum period, but pre-existing OCD was exacerbated equally during pregnancy and the postpartum period in the range of 20%–50%. Specific symptoms during pregnancy and the postpartum period include obsessions about contamination or aggression toward the child, leading to compulsive cleaning, avoidance of the infant, and/or excessive checking on the well-being of the infant.[16] The literature is also recognizing that woman can develop *posttraumatic stress disorder* (PTSD) from trauma experienced during pregnancy or childbirth, and the prevalence is estimated at 1%–2%, which may be higher in low-income countries.

A Brief Treatment Overview of Psychiatric Disorders in the Postpartum Period

In general, psychiatric disorders during the postpartum period require the same standard treatments as during the non-postpartum period, except that consideration must be given to the safety of these medications during lactation. Sleep deprivation needs to be prevented in postpartum mothers with psychiatric disorders, and this may require either the suspension of breastfeeding if the nursing intervals are too frequent or the supplementation of breastfeeding with formula or pumped breast milk with the assistance of other caregivers.

"Postpartum blues" typically do not require treatment beyond psychosocial support and reassurance. Treatment of postpartum major depression should be comprehensive, utilizing both psychotherapy and psychopharmacology. Interpersonal and cognitive behavior therapies have been shown to be effective forms of treatment.[17] Antidepressants can be prescribed for postpartum depression, and overall, the same general principles apply as with other types of major depressive disorder. Nursing should not be discouraged unless a complicating factor, such as psychosis, suicidality, or infanticide risk, is present. Patients should also be reminded that *electroconvulsive therapy* (ECT) is always an option and that it has the highest rates of response and remission of any antidepressant treatment at 70%–90%. This is consistent with the 2010 American Psychiatric Association guidelines on the treatment of major depressive disorder.[18]

Regarding the treatment of postpartum bipolar disorder, standard treatments for bipolar disorder (mood stabilizers and atypical antipsychotics) should be utilized, with consideration given to their safety during lactation. Additionally, women should be educated on optimizing sleep during the postpartum period to avoid precipitating an episode of mania. The use of prophylactic mood stabilizers should be continued in the postpartum period, as bipolar disorder has a high risk of relapse when medication is discontinued. If the mood stabilizer had been stopped during pregnancy, it must be restarted immediately after birth, as manic symptoms can recur within three to four days postpartum.

Mothers with postpartum psychosis should be hospitalized, given the high risk of infant neglect, infanticide, and suicide. Antipsychotics and mood stabilizers should be utilized as clinically indicated. In general, mothers with postpartum psychosis should not breastfeed given the clinical severity of affective and psychotic symptoms that usually necessitate inpatient care and given the possibility of the risk of self-harm. Breastfeeding may be resumed after clinical stabilization.

Bergink et al.[19] introduced a four-step algorithm to be used in patients with first-onset postpartum psychosis or mania. By using this treatment method, the authors found that 98.4% of their patients achieved complete remission in the first three steps. At nine months postpartum, the sustained remission was 79.7%. The four steps are as follows: (1) begin treatment with lorazepam at bedtime for three days, (2) begin antipsychotic medication (haloperidol [Haldol] at 2–6 mg per day is recommended) on day four if symptoms continue, (3) add lithium for those who do not have a significant clinical response with a target plasma level of 0.8–1.2 mmol/l after two weeks of treatment with both a benzodiazepine and an antipsychotic, and (4) administer ECT to those who do not respond after 12 weeks to the above triple therapy.

The Effects of Psychiatric Illness on Mothers and Infants:

There has long been a general consensus among both psychiatrists and obstetricians that perinatal and postnatal mental illness has detrimental effects on the fetus and the child. Interaction difficulties between depressed mothers and their children are universal across all cultures and socioeconomic status groups.[20] Meta-analysis data has shown that there is a correlation between perinatal mental illness and obstetrical complications, such as pre-eclampsia, low Apgar scores, and *neonatal intensive care unit* (NICU) admissions; there is, however, no known causation. It is hypothesized that hyper- or hypoactivity of the *hypothalamic–pituitary–adrenal* (HPA) axis may affect uterine artery blood flow, fetal developmental growth, and parturition.[21] **Both antenatal and postpartum depression have been linked with insecure attachment of the disorganized type.** There is an increased risk of poor cognitive outcomes

with postpartum depression when compared to antenatal depression, including a very small decrease in IQ scores.[22]

A meta-analysis of studies on early interactions between mothers and infants shows that mothers with postpartum mental illness were more irritable, hostile, and less engaged with their infants and displayed overall decreased emotions and warmth toward their infants. They even showed decreased rates of play, which can delay the development of social and motor skills in infants. Non-depressed mothers engage in face-to-face play and smiling such that infants learn healthy communication skills, and these behaviors are fewer in depressed mothers. These infants later show less expressive language skills and decreased performance on measures of cognitive-linguistic functioning.[20]

Longitudinal studies have shown that in the children of mothers experiencing antenatal depression, there is an increased risk of emotional problems during childhood and an increased incidence of depressive episodes during adolescence. Some studies have even shown that male infants of mothers with depression are more vulnerable than female infants to high levels of maternal depressive symptoms.[20] Postpartum depression has been shown to increase the risk of depression and *attention-deficit hyperactivity disorder* (ADHD) in children up to 16 years old. Unfortunately, maternal education and support have only been shown to improve associations between postpartum depression and poor childhood outcomes, but have not been shown to improve antenatal depression.[22]

Infanticide is perhaps the most drastic consequence of postpartum psychiatric illness and is most often associated with postpartum psychosis. More than half of mothers with postpartum depression reported thoughts of wanting to harm their infant, fear of being alone with their infant, and fear of their inability to care for their infant.[20]

Table 1:
Negative Effects of Peripartum Psychiatric Illness on the Mother–Child Dyad

- Irritability in the mother and decreased emotional bonding with the infant
- Problems with breastfeeding
- Reduced use of safety practices, such as car seats
- Lower rates of preventive healthcare utilization and vaccination
- Insecure attachment of the disorganized type in the infant
- Negative impact on cognition and language development
- Decreased rates of play in the infant
- Delayed development
- Increased risk of emotional problems in childhood
- Increased risk of depression in adolescence
- Infanticide
- Suicide

The Pregnancy and Lactation Labeling Rule (PLLR)

In December 2014, the FDA published the new PLLR, which took effect on June 30, 2015. This changes the current prescription drug labeling system (A, B, C, D, and X) to a new system that is intended to help healthcare providers better understand the risks and benefits of medication use during pregnancy and lactation and communicate this to their patients more appropriately. New medications approved after June 2015 no longer have the old safety categories, and there is a minimum of three years to submit updated information to meet the requirements of the PLLR for all drugs approved after June 30, 2001.[23] The first regulations were introduced in the US in 1962 in response to the use of thalidomide during pregnancy, which led to at least 17 cases of fetal limb abnormalities. Critics of the ABCDX labeling system have long pointed out that not all drugs within the same category have the same risk, and the categories are often misleading, especially for medications for which no human data exists.

The new labeling includes three updated categories: "pregnancy" (information regarding pregnancy exposure), "lactation" (the amount of a drug that is transferred in breast milk and potential effects on the infant), and "females and males of reproductive potential" (contraception recommendations and information about infertility). The lactation section includes information on how much of a drug is secreted in breast milk and how this amount compares to blood concentrations. This information will be used to determine how much of the drug is consumed by the infant. Under each of these categories, there is a general outline for each drug that includes whether or not a registry for the drug exists, a general background risk statement, clinical considerations (with prescribing

decision-making suggestions for providers), and a summary of the available data from trials (human and animal data will be presented separately).[24]

General Principles of Psychotropic Use During Lactation:

- Use the lowest effective dose and avoid polypharmacy where possible.
- Where practical, breastfeeding can be timed to avoid peak drug levels in the milk, or the milk can be expressed for subsequent feeding.
- The benefits of breastfeeding for the mother–infant dyad must be weighed against the risks of harm to the infant from medication exposure on a case-by-case basis. The infant is at risk of exposure to medication side effects and the effects of untreated psychiatric illness of the mother. Clinical decision making should take both these exposures into account.
- All infants of lactating mothers receiving psychotropic medications should be monitored for any general and 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 premature infants and infants with renal, hepatic, cardiac, or neurological impairments, as they are at a greater risk of side effects, even from low levels of medication exposure.
- In general, treatment for 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 cease the 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/discontinuation symptoms in the infant.
- Take into consideration how the effects of a medication could affect the mother's ability to care for her baby.
- Psychiatric medications for which there is more published data regarding safety should be preferred over recently marketed medications, unless clinically indicated otherwise.
- Where possible, medications with short half-lives, high protein binding, low oral bioavailability, and high molecular weight should be preferred.
- Psychotropics with long pediatric half-lives should be used very cautiously, given the risk of build-up in an infant's plasma over time.
- Acknowledge the maternal caregiver role and respect the mother's preferences with regard to lactation without judgment.
- Offer psychological interventions to all patients who choose not to continue psychotropic medication during lactation.
- Measuring serum levels of the psychotropic medications in the infant is not routinely recommended.

Pharmacokinetics in Lactation

Drugs generally enter a mother's milk through a process of passive diffusion due to the concentration difference between the maternal plasma compartment and the milk compartment. The maternal plasma concentration of the medication therefore becomes a crucial determinant of drug penetration. To diffuse into the milk compartment, drugs have to pass through bilayer lipid membranes of the lactocytes. Lipid-soluble drug molecules are better able to move across these membranes. (In the first three days postpartum there are large gaps between lactocytes facilitating the transfer of maternal immunoglobulins and other proteins, which also allows the transfer of most drugs. Nonetheless, the absolute dose of the medications during this period is still low as the rate of milk production is lower in the first few days.[25]) Some cellular pumps that actively transfer drug molecules into the milk have been identified, most important of which is iodine.

However, transfer by cellular pumps is not a significant mechanism for the lactational transfer of psychiatric medications.

Weakly basic drugs with high pKa (e.g., barbiturates) can become trapped in the milk compartment after diffusion because the relatively lower pH of human milk changes the ionic state of the drugs. Drug molecules in the maternal plasma circulate either bound to albumin or circulate freely. It is the unbound fraction of the circulating drug molecules that is transferred into the milk; therefore, medications with low protein binding are present in higher concentrations in the milk.

Medications transfer easily into human milk if there is a high concentration in the maternal plasma, if they have a low molecular weight, if their protein binding is low, and if they are lipid-soluble.[25]

Once medication is present in the milk, several other pharmacokinetic considerations come into play. The primary consideration is the oral bioavailability (the percentage of a drug that reaches the systemic circulation after oral administration) of the medication to the infant. The medication may be poorly absorbed or may be metabolized by the neonatal liver. The glucuronidation and oxidation systems are immature at birth (they can be functioning at a level as low as 20% of adult levels). Additionally, rates of glomerular filtration and tubular secretion are also significantly lower, which could potentially result in higher-than-anticipated psychotropic exposure for the newborn.[26]

Some of the pharmacokinetic parameters of importance with respect to lactation include the half-life of the medication, the time interval from the time of medication administration to the time of peak level in the mother's plasma, the percentage of maternal protein binding, oral bioavailability, the *milk-to-plasma* (M/P) ratio, and the *relative infant dose* (RID).[25] The M/P ratio is the concentration of medication in the mother's milk divided by the concentration in the mother's plasma. M/P ratio greater than 1.0 is indicative that the drug is present in breast milk in concentration higher than the concentration in mother's plasma. However, the absolute amount of drug transferred would depend on the concentration in the mother's plasma. Therefore, even a medication with a high M/P ratio would be present in milk in low amounts if the concentration in the mother's plasma is low. Therefore, M/P values by themselves can be misleading. A better indicator is the RID, which is the daily dosage of the drug received by an infant via breast milk (mg/kg/day) expressed as a percentage of the weight-adjusted maternal daily dose (mg/kg/day). A cut-off RID value of 10% is increasingly being accepted to imply that the medication is compatible with breastfeeding. However, values higher than 10% do not necessarily indicate that a medication is incompatible with lactation. Another way of quantifying infant drug exposure is to express the infant serum concentration of the medication as a percentage of the maternal serum concentration. Using this quantifying factor, in a clinical report,[27] the American Academy of Pediatrics provided a list of psychiatric medications with infant serum concentrations exceeding 10% of maternal plasma concentrations during breastfeeding. This list consisted of *citalopram* (Celexa) *clomipramine* (Anafranil), *diazepam* (Diastat, Valium), *doxepin* (Silenor, Zonalon, Prudoxin), *fluoxetine* (Sarafem, Prozac), *fluvoxamine* (Luvox, Faverin, Fevarin, Floxyfral), *lamotrigine* (Lamictal), *lithium* (Lithobid, Lithane), *mirtazapine* (Remeron, Remeronsoltab), *nortriptyline* (Pamelor), *olanzapine* (Zyprexa), *sertraline* (Zoloft), and *venlafaxine* (Effexor). It is pertinent to mention here that majority of these medications are regularly prescribed for use during breastfeeding by clinical experts in this field with no appreciable side effects.

The ideal characteristics of a psychotropic suitable for lactation are a short half-life, high maternal protein binding, a low M/P ratio, low RID, and low infant serum concentration compared to maternal plasma concentration. While helpful in theory, in practice, the lactational risk associated with psychotropics in the existing literature has been determined largely based on reported (and often isolated) adverse events; clinical lactational risk cannot be predicted based on knowledge of pharmacokinetic data alone.[28]

The pharmacokinetics of medication transfer in breast milk involve the two well-recognized excretion gradients of distribution and time.[26] Because psychotropic medications are lipophilic, they are present in greater concentrations in the fatty hindmilk and in lesser concentrations in the foremilk. Owing to the distribution gradient, the M/P ratio calculated from a random breast milk sample can give an inaccurate estimation. The time

gradient gives information about the relationship between medication ingestion by the mother and the time of peak breast milk concentrations for that medication, which depends on the rate of gastrointestinal absorption of the medication. For instance, for sertraline, the peak breast milk concentration occurs approximately eight hours after the most recent dose, while the lowest concentration occurs just prior to the next dose.[26] Knowledge of the time gradient can be utilized to decrease infant medication exposure by timing the breastfeeds at times when the drug concentration in the milk is expected to be low.

Table 2:
Important Pharmacokinetic Parameters in Lactation

Milk-to-Plasma (M/P) Ratio: the ratio of the concentration of medication in mother's milk divided by the concentration in mother's plasma

Relative Infant Dose (RID): the daily dosage of the medication received by an infant via breast milk (mg/kg/day), expressed as a percentage of the weight-adjusted maternal daily dose (mg/kg/day)

The infant serum concentration of medication is expressed as a percentage of the maternal serum concentration.

Psychotropics and Lactation

The discussion below presents a summary of the most pertinent clinical issues related to the use of respective psychotropic medications during lactation. It is not meant to be exhaustive; for a more comprehensive discussion of particular psychotropic medications, consult the Drugs and Lactation Database,[29] which is part of the National Library of Medicine's Toxicology Data Network. It is updated monthly and is peer reviewed for accuracy. It is important to mention that there is a significant dearth of high-quality research in this area, with most of the side effects being reported in isolated case reports, and given the lack of large-scale studies and controlled trials, the rates of the reported side effects are unknown and are expected to be very low. A literature discussion that relies heavily on isolated case reports, as the discussion on the safety of psychotropics in lactation usually is, becomes biased towards the negative because the few cases of adverse events are highlighted, while the millions without adverse events go unrecognized in comparison. Therefore, in this review we have generally chosen not to include adverse events reported in single case studies.

Antidepressants:

Selective-serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine

Fluoxetine (along with its active metabolite norfluoxetine) is present in breast milk in relatively higher amounts compared to other SSRIs. Due to its longer half-life, it is also more likely to accumulate in breastfed infants. Widespread clinical use has established the safety of fluoxetine in lactation colic; decreased sleep, vomiting, watery stools, hyperactivity, and decreased arousal have been reported in isolated case reports, but the rates of these effects are not known and are expected to be clinically very low.[29] Where possible, other antidepressants with lower breast milk excretion should be preferred during lactation, but if required, fluoxetine can be used with caution.

Fluvoxamine

Infant serum levels of fluvoxamine are generally undetectable, although one case of an infant serum level greater than 10% of the mother's has reported.[30] No adverse effects, including effects on neurobehavioral development, have been reported.

Paroxetine and Sertraline

Paroxetine (Pexeva, Paxil) and sertraline have low levels in breast milk and are generally undetectable in infant serum. They can generally be used during lactation without adverse effects, although irritability and feeding problems have been reported with paroxetine, and hypotonia, drowsiness, growth disturbance, and withdrawal symptoms on cessation of feeding have been reported with sertraline.[29] **Paroxetine and sertraline are considered by many reviewers to be two of the preferred antidepressants for use during lactation;** however, clinically, it should be recognized that paroxetine has the worst withdrawal symptoms among the SSRIs. Sertraline is also the only psychotropic with an L1 lactation risk category (extensive data, compatible) as of 2015, according to Hale.[25]

Citalopram

Low infant serum levels of citalopram have been reported to be detectable in some infants. Poor suckle, drowsiness, and sleep disturbance have been reported.[31] However, adverse effects in infants are comparable to controls,[32] and normal neurobehavioral development up to one year has been reported.[33]

Escitalopram

Limited available data indicates that *escitalopram* (Lexapro) should be preferred over citalopram during lactation due to lower levels in breast milk and the lack of reported adverse events.[29]

Serotonin–norepinephrine Reuptake Inhibitors (SNRIs)

No adverse effects have been reported in infants with the use of venlafaxine, *desvenlafaxine* (Pristiq), and duloxetine during lactation. Duloxetine in breast milk is low and infant serum levels are undetectable to low. Both venlafaxine and desvenlafaxine are present in breast milk in relatively higher amounts, with desvenlafaxine exposure of breastfed infants being about half of the total drug exposure of breastfed infants compared to venlafaxine.[29] Infant serum levels are less than 10% for desvenlafaxine but can be higher than 10% for venlafaxine.

Tricyclic Antidepressants (TCAs)

For decades, TCAs have been used during lactation with safe outcomes. In general, the infant serum levels for TCAs are undetectable to low. Side effects in infants have not been reported with the use of *amitriptyline* (Pamelor), clomipramine, *desipramine* (Norpramin), *dosulepin* (Prothiaden, Dothep, Thaden), *imipramine* (Tofranil), *mianserin* (Lumin, Tolvon), and nortriptyline in lactation. Doxepin is an exception among TCAs in this regard due to its sedating effects, long half-life, high infant serum levels, and two reported cases of respiratory depression.[30, 34] There is a universal recommendation among reviewers to avoid doxepin during lactation, especially as other safer alternatives are available.[25,26,28,29,34,35] It carries a Hale's lactation rating of L5 (limited data, hazardous).[20] Of the TCAs, some reviewers prefer nortriptyline for use during lactation.[34, 35]

Monoamine Oxidase Inhibitors (MAOIs)

There is little to no published literature establishing the safety of MAOIs during lactation. Additionally, the clinical use of MAOIs is complicated by significant drug interactions and dietary restrictions. Therefore, MAOIs are not preferred for use during lactation.

Other Antidepressants

Bupropion

Bupropion (Wellbutrin, Buproban, Aplenzin) has low levels in breast milk and side effects have not generally been reported, except for a case of seizure in a six-month-old infant consistent with its seizure- lowering potential.[36]

Mirtazapine

Mirtazapine (Remeron) is generally present in low concentrations in breast milk, and no adverse events with its use have been reported.

Trazodone

Trazodone (Oleptro) drug levels in milk are low, and no adverse effects have been reported.

Mood Stabilizers:

Lithium

Lithium use during the first trimester of pregnancy has been associated with a teratogenic risk of cardiac malformations, characteristically the Ebstein anomaly (a malformation of the tricuspid valve and right ventricle), which occurs in 1 in 1000 births with lithium exposure.[38] Its use during the second and third trimesters can lead to a number of neonatal complications, such as premature labor, polyhydramnios, cardiomegaly, hepatomegaly, nephrogenic diabetes insipidus, goiter and hypothyroidism, and gastrointestinal bleeding.[38] It can also result in "floppy infant syndrome" in neonates secondary to lithium toxicity, manifesting as flaccidity, lethargy, poor suckling, low Apgar scores, shallow breathing, and apnea. Holding lithium 24–48 hours prior to delivery (in case of planned induction) and resuming after delivery when the mother is medically stable can help minimize the infant's serum lithium concentration at birth, decreasing the risk of neonatal toxicity.[39] Treatment with lithium during pregnancy often requires an elevated dose because maternal

renal clearance is increased. After delivery, maternal renal clearance returns to baseline levels, and maternal lithium levels therefore require close monitoring.

Lithium is present in breast milk in relatively higher amounts compared to other psychotropic medications. The M/P ratio varies from 24%–66%. The RID is 12%–30%. Infant serum levels are usually within the range of 10%–50% of maternal serum concentrations,[40, 41] but this range can be as wide as 5%–200%.[34]

Numerous side effects in infants with lithium exposure via lactation have been reported in the literature, including hypotonia, lethargy, hypothermia, cyanosis, and electrocardiogram changes.[41, 42] However, in multiple studies, lithium has been well tolerated by breastfed infants with no signs of toxicity or behavioral and developmental effects.[29,43]

Due to lithium's high concentrations in breast milk and high infant serum levels and the reported adverse effects and potential for serious toxicity, lithium has traditionally been considered to be incompatible with breastfeeding. However, other sources have argued for a cautious rehabilitation of lithium use during lactation based on evidence from multiple studies where breastfed infants did not experience significant adverse effects. This is particularly the case when the infant is healthy and is being regularly monitored.[28] The American Academy of Pediatrics[44] has classified lithium as a medication associated with significant effects on some nursing infants that should be administered to nursing mothers with caution. It has a Hale's lactation category of L4 (significant data—possibly hazardous).[25]

Some authors have recommended monitoring infant serum lithium, serum creatinine, *blood urea nitrogen* (BUN), and *thyroid-stimulating hormone* (TSH) every 4–12 weeks during breastfeeding,[43,45] but other sources have recommended obtaining infant serum lithium levels and utilizing laboratory monitoring only if concerns arise during clinical monitoring.[46]

The hydration status of the infant has dramatic effects on lithium levels, and dehydration can result in significant lithium toxicity. The hydration status of nursing infants should therefore be carefully monitored during maternal lithium therapy.

Valproic Acid

Valproic acid is present in low concentrations in breast milk and infant serum, and no side effects have been reported. Its use during lactation is generally considered safe. Some authors recommend periodic monitoring of serum valproate levels, blood counts, and liver enzymes in nursing infants,[47] but the recommendation is not universal. Although safe during lactation, there are significant fetal risks associated with the use of valproic acid during pregnancy.[38]

Carbamazepine

Carbamazepine (Tegretol, Carbatrol, Equetro) is present in breast milk in relatively high levels with detectable infant serum levels, but its use during lactation is generally considered safe. The vast majority of infants do not experience any adverse effects. Poor suckling, decreased weight gain, sedation, and spasms have been observed after the cessation of breastfeeding; however, the rates of these effects are unknown and likely to clinically very low.[31,34] Infants should be clinically monitored for jaundice and signs of hepatic dysfunction. The monitoring of blood counts, serum liver enzymes, and serum carbamazepine levels in infants has been recommended.[47] Similar to valproic acid, carbamazepine use is safe during lactation, but there are significant fetal risks associated with its use during pregnancy.[38]

Lamotrigine

Lamotrigine (Lamictal) has high infant plasma levels (up to 50% of maternal levels), and neonates have a low ability to metabolize the drug.[29] Benign thrombocytosis, irritability, poor feeding, and respiratory sedation have been reported.[31,34] Lamotrigine can cause a life-threatening rash in adults and children, with a higher risk in the pediatric population.[48] This has not been reported so far in breastfed infants.

Typical Antipsychotics:

Infant exposure to typical antipsychotics via lactation is generally clinically insignificant. Most studies have reported no adverse effects. Three infants exposed to a combination of haloperidol and chlorpromazine were reported to have delayed development,[49] but other

studies have reported no developmental delays with *haloperidol* (Haldol) and *chlorpromazine* (Thorazine).[34,50] Chlorpromazine was associated with lethargy in one infant, but no side effects have been noted for haloperidol, *flupenthixol* (Depixol, Fluanxol), *perphenazine* (Trilafon), *trifluoperazine* (Eskazinyl, Eskazine, Jatroneural), *zuclopenthixol* (Cisordinol, Clopixol, Acuphase), *sulpiride* (Dogmatil), and amisulpride.[34,51]

Atypical Antipsychotics:

As with typical antipsychotics, the transfer of atypical antipsychotics through breast milk to infants is low and clinically insignificant. There is a paucity of published literature on the use of atypical antipsychotics in lactation, but no recurring adverse effects have been reported in infants exposed to olanzapine, aripiprazole, risperidone, quetiapine, and ziprasidone.[34, 51]

Sedation and excessive accumulation of clozapine in breast milk have been reported,[31] but the rates are unknown. Due to clozapine's potential to cause agranulocytosis, some authors are wary of its use during lactation.[29, 51] As clozapine is most often used for treatment-resistant schizophrenia after other antipsychotics have failed, in situations warranting concern, it is more feasible to discontinue breastfeeding than to discontinue clozapine.

Sedatives and Hypnotics:

Benzodiazepines

There is a risk of *central nervous system* (CNS) depression and apnea with lactational exposure to benzodiazepines, although the risk is generally low. In one study of 124 mothers treated with benzodiazepines (mostly *lorazepam* [Ativan], *clonazepam* [Klonopin], and *midazolam* [Dormicum, Hypnovel]), sedation was noted in two infants (1.6%).[52] Sedation has been reported with diazepam use,[31] and sedation and withdrawal symptoms have been reported with alprazolam use.[31]

Neonates metabolize benzodiazepines slowly, and benzodiazepines therefore accumulate in neonates who receive continued exposure through lactation. **Benzodiazepines with longer half-lives, such as diazepam, are not recommended for use during lactation for that reason.** Lorazepam has no active metabolites and is preferable in low doses. When used judiciously, benzodiazepines are safe during lactation, and single doses should not require any limitation on breastfeeding. However, all infants exposed to benzodiazepines should be monitored for signs of CNS depression, and breastfeeding should be discontinued if signs of toxicity, such as sedation, reduced suckling, or respiratory depression, are noted.

Other Hypnotics

Limited published literature appears to indicate that *zaleplon* (Sonata), *zolpidem* (Edluar, Ambien, Zolpimist), and zopiclone are safe to use during lactation.[31,51]

Table 3:
Psychotropic Medications and Lactation: Summary of Concerns

Antidepressants
- Fluoxetine has a longer half-life and is more likely to accumulate.
- Doxepin has been linked to sedation and respiratory depression in infants. Its use is contraindicated during lactation.
- Avoid MAOIs given the significant drug interactions, dietary restrictions, and lack of safety literature.
- Bupropion can lower the seizure threshold.

Mood Stabilizers
- Lithium is present in milk in high amounts and has the potential for toxicity. Administer with caution during lactation, with regular clinical and laboratory monitoring of the infant.
- Lamotrigine has the potential to cause a life-threatening rash. Monitor and immediately discontinue with any appearance of a rash.

Antipsychotics
- There is limited data for antipsychotics in general, but there are no significant safety concerns except for clozapine, which can potentially lead to agranulocytosis.

Benzodiazepines
- Benzodiazepines can accumulate in neonates due to immature hepatic (cytochrome P450) enzymes.
- There is a risk for CNS and respiratory depression. Monitor clinically.
- Avoid benzodiazepines with long half-lives, such as diazepam.

Conclusion

The prevalence of psychiatric disorders during the postpartum period is at least comparable to that of the general population, with some indication that the first five weeks after childbirth are a vulnerable period for the onset of psychiatric illness. Additionally, there are significant detrimental effects of psychiatric illness on the mother and infant. These include a negative impact on bonding with the infant, reduced cognitive and language development, insecure attachment, increased risk of depression for the child in childhood and adolescence, suicide, and infanticide. All psychotropic medications are secreted in breast milk, but the majority are present only in low concentrations and can be used safely in lactating mothers. Medications that warrant further caution include fluoxetine (risk of accumulation), doxepin (respiratory depression), MAOIs (complicated clinical use and lack of safety literature), lithium (high breast milk concentration, potential for toxicity), and benzodiazepines (CNS and respiratory depression).

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Multiple-Choice Questions

57. Which of the following is *true* with regard to the risk of psychiatric illness in the postpartum period?

A. A prior history of depression does not increase the risk of subsequent development of postpartum depression.

B. Primiparity is an obstetric risk factor strongly associated with developing postpartum psychosis.

C. Most cases of postpartum psychosis are believed to be cases of schizophrenia.

D. Pregnancy and the postpartum period have been shown to be "protective periods" for mental health, with lower incidence and prevalence of psychiatric disorders.

58. Which of the following is *false* with regard to the consequences of psychiatric illness in the postpartum period?

A. Infanticide is more often associated with postpartum psychosis, but women with postpartum depression also report thoughts of wanting to harm their infants.

B. Postpartum depression has been shown to increase the risk of emotional problems beyond childhood years and even into adolescence.

C. Both antenatal and postpartum depression can lead to insecure attachment of the disorganized type.

D. Children of depressed mothers have higher rates of preventive healthcare utilization.

59. Which of the following is *true* regarding the use of antidepressants and mood stabilizers during lactation?

A. Paroxetine and sertraline are the preferred antidepressants for use during lactation.

B. Fluoxetine has a short half-life and is less likely to accumulate in infants.

C. There are no reported cases of seizures in infants exposed to bupropion through lactation.

D. The hydration status of the infant does not significantly influence lithium levels in the neonate during breastfeeding.

60. Which of the following is *false* regarding the use of antipsychotics and sedatives/hypnotics during lactation?

A. Infant exposure to typical antipsychotics via lactation is generally low, and most studies report no adverse effects.

B. Clozapine has the potential to cause agranulocytosis in the infant due to exposure via breast milk.

C. There is no significant risk of CNS depression and apnea with exposure to benzodiazepines because they are not found in high concentrations in breast milk.

D. Benzodiazepines with short half-lives are preferred for use during lactation.

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Best Practices in CME

Psychiatric Disorders and Psychotropic Treatment in the Postpartum Period

Asim A Shah, MD; Awais Aftab, MD; and Samantha Latorre, MD

ID#: L003358

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to psychiatrists, family physicians, and obstetricians who require information on the prevalence of psychiatric disorders in the postpartum period, the negative effects of psychiatric illness on the mother and infant, and the psychopharmacological treatment of postpartum or lactating patients with psychiatric disorders.

Key Point 1: Risk of Psychiatric Disorders in the Postpartum Period

Evidence strongly indicates that the prevalence of psychiatric disorders during pregnancy and the postpartum period is at least comparable to that in the general population, with some indication that the first month after childbirth is particularly high risk for the onset of depression and psychiatric admission.

Key Point 2: Effects on Psychiatric Illness on Mother and Infant

There are significant detrimental effects of untreated psychiatric illness on the mother and infant. These include the negative impact on bonding with the infant, reduced cognitive and language development, insecure attachment, increased risk of depression for the child in childhood and adolescence, suicide, and infanticide.

Key Point 3: Pharmacokinetics in Lactation

The ideal characteristics of a psychotropic suitable for lactating women are short half-life, high maternal protein binding, low milk-to-plasma ratio, low relative infant dose, and low infant serum concentration compared to maternal plasma concentration.

Key Point 4: Psychotropic Medications and Lactation

All psychotropic medications are secreted in breast milk, but the majority are present only in low concentrations and can be used safely in lactating mothers. Medications that warrant further caution include fluoxetine, doxepin, MAOIs, lithium, and benzodiazepines.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Depression: An Overview and Diagnostic Changes in the DSM-5

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

KEY WORDS: Depression • Neurobiology • Diagnosis • DSM-5

LEARNING OBJECTIVES: At the end of this lesson, clinicians will be able to: (1) recall the high global prevalence of depression with its attendant morbidity, (2) review the various types of depression along with its underlying neurobiology, (3) examine the ways in which depression may present in clinical practice, and (4) classify depression according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and contrast the changes with the same manual, fourth edition, text revision (DSM-IV-TR).

LESSON ABSTRACT: Depression is a global, highly prevalent illness with significant medical comorbidity and high personal and social costs. The underlying mechanisms of depression are gradually being elucidated, although much remains to be done. The DSM-5 with its stated goal of finding common ground with the *International Classification of Disease* (ICD-11) has reclassified several types of depression and eliminated others. Important changes include the bereavement exclusion in depression, and changes in the diagnostic criteria for dysthymia. In this lesson, we review the epidemiology and global disease burden of depression, briefly examine the types and their underlying neurobiology, and compare the changes in the diagnostic criteria for depression in the DSM-5 to its predecessor (DSM-IV-TR). Two case studies are included to help clinicians familiarize themselves with the new diagnostic criteria.

COMPETENCY AREAS: This lesson will allow clinicians to employ evidence-based diagnostic practice in the treatment of depressive illness to improve the quality of care they provide to their patients as well as improve their medical knowledge about this illness.

Introduction

Depression is a common, highly debilitating illness with a lifetime prevalence of up to 20%.[1] The *World Health Organization* (WHO) has ranked depression the fourth leading cause of disability worldwide.[2] By 2020, depression is projected to be the second leading cause of disability worldwide.[3] According to WHO, more than 350 million people of all ages suffer from *major depressive disorder* (MDD) globally, and about 20 million of those live in the US. The U.S. *Centers for Disease Control and Prevention* (CDC) [4] 2006 and 2008 surveys of 235,067 adults form 45 states plus the District of Columbia, Puerto Rico, and the U.S. Virgin Islands found the rate of current depression (using the *Patient Health Questionaire-8* [PHQ-8]) to be 9% and the rate of those with a current diagnosis of major depression according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), criteria to be 3.4%.[5]

In addition to being a significant cause of morbidity, depression can also worsen the health outcomes of other chronic illnesses, such as angina, asthma, diabetes, and arthritis.[6] Depression is frequently associated with functional impairment, psychosocial disability, and absenteeism and reduced productivity at work.[7, 8] **The typical burden of depression is fivefold: residual symptoms of depression, cognitive impairment, reduced quality of life, and the recurring nature of the illness. In addition, depression increases the risk of mortality from multiple illnesses (see below), causes significant disability related to work and psychosocial issues, disrupts family functioning, and results in significant economic losses to the individual and society.[9]**

Increased Mortality Risk

Untreated depression greatly increases the risk of suicide. The *standardized mortality ratio* (SMR) for suicide in patients with unipolar depression is 20.9 in men and 27.0 in women; that is**, the risk of completed suicide for patients with depression is more than 20 times higher than the risk for the general population.[10] Emerging data also cite untreated depression as a major risk factor for many medical illnesses.** For example, the risk of dying from an initial myocardial infarction is higher in patients with depression and varies with the severity of the depressive episode, and clinically severe depressive symptoms significantly increase the risk of death from cardiovascular disease and stroke.[11] A meta-analysis of 20 studies showed that clinical depression is a significant risk factor for mortality in patients with coronary heart disease short-term (3–6 months; adjusted odds ratio 2.07) and long-term (6–24 months; adjusted odds ratio 2.61).[12]

Functional and Family Burden

Data from the National Comorbidity Survey Replication, a U.S. nationally representative household survey, showed that overall impairment is significantly higher for mental disorders than for chronic medical disorders. Severe functional impairment was reported by 42% of persons with mental disorders and 24% with chronic medical disorders.[13] Taking into account absenteeism and presenteeism (being physically present at work but functioning suboptimally), an average of more than 27 workdays per year are lost per employee with depression, representing an annual individual loss of US $4400. At the national level, this translates into a loss of US $36.6 billion per year in the US.[14]

Depression is common in pregnancy. Ten to sixteen percent of pregnant women fulfill the diagnostic criteria for *major depression* (MD), and even more women experience subsyndromal depressive symptoms.[15] Maternal depression can cause numerous complications for a developing fetus or newborn, including spontaneous abortion, preterm delivery, low birth weight, lower Apgar scores at birth, delays in cognitive development, etc.[16]

Prompt diagnosis as well as urgent and effective treatment is therefore essential for all patients with depressive illness.

Types of Depression

The DSM-5:

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the *American Psychiatric Association* (APA),[17] offers a common language and standard criteria for the classification of mental disorders. The manual is used by a multitude of personnel and organizations, including, but not limited to, clinicians, researchers,

psychiatric drug regulation agencies, health insurance companies, pharmaceutical companies, the legal system, and policy makers. An alternative system produced by WHO is called the *International Statistical Classification of Diseases and Related Health Problems* (ICD).

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), classifies depressive illness into several subtypes. Excluding the new pediatric category of disruptive mood dysregulation disorder (discussed in the last section of this lesson), **the subtypes are MDD, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder.[16] The DSM-5 has separated depressive disorders from depression that occurs in the context of bipolar illness. All of the conditions subsumed under the category of depressive disorders share the core central feature of sad or irritable mood plus somatic or cognitive symptoms that negatively impact a person's functioning.**

MDD is the classic condition in this group and is characterized by affective, cognitive, and neurovegetative symptoms lasting a minimum of 2 weeks. In most cases, the duration of symptoms is considerably longer. Single episodes may occur although recurrence is the norm. The DSM-5 has removed the bereavement exclusion, which allows clinicians to diagnose MDD within the first 2 months following the death of a loved one. The bereavement exclusion has been removed to facilitate early recognition and treatment of MDD in a bereaved person.

A chronic form of depression, persistent depressive disorder (dysthymia) can be diagnosed in adults with depressive symptoms that persist for 2 years or more (1 year in children). After extensive research over the last 20 years, premenstrual dysphoric disorder has been moved from an appendix of the DSM-IV to Section II classification of the DSM-5. Persistent depressive disorder (dysthymia) is now recognized as a specific, treatment-responsive form of depressive disorder that begins sometime following ovulation, remits a few days after the menstrual cycle starts, and significantly impacts functioning. Multiple medications, substances of abuse, and medical conditions can cause depressive symptoms, and these subtypes are listed under depressive disorders secondary to substance abuse of medication use or secondary to a specific medical condition.

Two other nonspecific depressive syndromes are also described in the DSM-5. Other specified depressive disorder indicates conditions resembling MDD that do not meet all criteria of the illness (e.g., recurrent brief depression) but for which the clinician chooses to specify the reason that the illness does not meet all criteria of a diagnosis and unspecified depressive disorder in which either there is insufficient information to make a diagnosis or the clinician chooses to not specify the reasons that criteria for a diagnosis are not met. The DSM-5 also includes multiple specifiers for depressive disorders based on symptom quality (e.g., with anxious distress, with melancholic features), severity (mild/moderate/severe), with or without psychosis, with seasonal variation.

The ICD-10:

An alternate classification system, WHO's *International Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10)[18] also separates depressive illness from bipolar disorder and classifies depressive illness as mild, moderate, or severe based on the occurrence of a combination of somatic (or biological) and cognitive symptoms, including (but not limited to) depressed mood, reduced energy, loss of interest, ideas of self-harm, and others. Clinicians can further specify whether the depressive episode is present with or without somatic symptoms or psychosis (in the case of a severe depressive episode). Recurrent depressive disorders follow the same criteria in the ICD-10. The ICD-10 also recognizes dysthymia or chronic depression and cyclothymia with repeated, mild fluctuations of mood. Several other categories recognize mood disorders that present some features of the syndromes outlined above but either do not meet the full criteria or present a mixed picture.

Efforts have been made to classify depression based on subsets of symptoms (Table 1), but there is, as yet, no evidence that they represent different disease states.

The operationalized, top-down approach of making a diagnosis of depressive illness in the DSM-5 and the ICD-10 in the absence of firm etiological or pathological foundations has led to some criticism,[19] for example, that many patients (sometimes the majority) end up in a not

otherwise specified category instead of a specific diagnosis or that some definitions of disorders are unstable with disappointing retest reliability.[20] However, pending new developments in etiology from, for example, genetics or neuroimaging research, this classification approach will continue to be predominant in clinical and research settings for the time being.

Neurobiology of Depression

For an illness that is so widespread and causes so much misery, we know surprisingly little about the underlying mechanism of depression, although the last decade has brought several exciting new discoveries.

Genetic Predisposition:

Although in other psychiatric syndromes, such as schizophrenia, researchers have identified numerous verified genetic loci that contribute to disease susceptibility,[21] the same cannot be said for depressive illness. Epidemiologic studies, including meta-analysis of high-quality family studies, indicate that the heritability of MDD is around 40%,[22] which makes it a highly heritable disorder similar to several common complex medical illnesses (type II diabetes, asthma, hypertension, certain cancers). However, MDD is a heterogeneous disorder in which, unlike schizophrenia, the majority of the genetic variance may be due to the joint effect of multiple loci of small effect.[23] **Increasing evidence now points to the fact that, similar to many psychiatric illnesses, depressive illness may be a basket of many different illnesses that share some clinical (and biochemical) features.[23]**

Neuroanatomy:

The circuitry underlying mood and emotion has been known at least since the 1930s when James Papez described a group of brain structures surrounding the brainstem (the cingulate gyrus, the hippocampus, the hypothalamus, and the anterior thalamic nuclei). This "system of emotion" was a description of a part of the limbic system that plays a vital role in learning, emotion, and memory, including cortical control of emotion.[24] Since then, neuroimaging techniques, including *magnetic resonance imaging* (MRI), *positron emission tomography* (PET), and *functional MRI* (fMRI), have helped elaborate and expand the importance of this "neurocircuit of emotion." In addition, other neighboring brain areas, including the prefrontal cortex and the amygdala, are now known to be intimately involved in the genesis of normal mood/emotional states as well as depressive illness.

Hypothalamic-Pituitary-Adrenal Axis:

Within the limbic system, the hippocampus is considered central in relation to depression because of the structure's fundamental role in learning and memory,[25] the fact that the hippocampus is rich in corticosteroid receptors[26] and is thus closely linked to the *hypothalamic-pituitary-adrenal* (HPA) axis (providing inhibitory feedback to it), and the fact that the hippocampus is one of two brain areas where neurogenesis continues to occur after maturity, making the area highly neuroplastic.[27] **There is evidence that hippocampal volume is reduced in recurrent depression, and patients who have remitted from their depressive illness have larger hippocampal volumes when compared with nonremitted subjects.[28]** There is also evidence that smaller hippocampal volumes in persons who are not depressed may predispose them to depression, for example, adolescents with early life adversity.[29]

Stressful life events have long been known to be triggers of depression in vulnerable persons.[30] Stress is also known to cause abnormalities in the HPA axis with elevated cortisol concentrations and dexamethasone nonsuppression in patients with depressive illnesses.[31] Sustained elevations of glucocorticoids, seen under conditions of prolonged, severe stress, can damage hippocampal neurons[32] that could reduce inhibitory control of the hippocampus on the HPA axis, further increasing glucocorticoid levels and hippocampal damage. These processes might be implicated in a subset of patients with depression and can be corrected with appropriate antidepressant treatment.

Immunological Mechanisms:

Several lines of evidence point to the involvement of the immune system in depression. Proinflammatory cytokines reliably elicit sickness behavior (fatigue, social withdrawal, lethargy), and symptoms of anxiety/depression as well as full-blown depressive illness are a well-known side effect for patients who receive treatment with interferon. Immune activation, particularly elevated cytokine concentrations, are a feature of severe depression. Impaired

glucocorticoid receptor function may be related to chronic exposure to inflammatory cytokines associated with chronic physical illness or chronic stress.[33] Resistance to glucocorticoids can lead to additional increases in inflammation and additional hippocampal damage.

Neurochemistry:

The earliest explanatory hypothesis of depressive illness, the monoamine hypothesis that attributes depressive symptoms to a deficiency of this or that neurotransmitter (and is portrayed in the public mind as chemical imbalance) is increasingly being superseded by attention to receptor changes at the synaptic and dendritic levels[34] and to new receptor targets such as *N-methyl-d-aspartate* (NMDA).[35]

Brain-derived neurotrophic factor (BDNF) present in abundance in the hippocampus appears to play a major role in neuronal growth, survival, and maturation. Stress suppresses the synthesis of the BDNF while antidepressant drugs increase its synthesis and its functioning.[36]

It appears then that depressive disorders have multifactorial etiologies that involve genetic predispositions as well as physical and psychological stress that operates via a number of mechanisms.

How Does Depression Present in Practice?

The following case studies will help clarify how depressive illness often presents in clinical practice.

Worthless:

Barbara,[a] a 34-year-old homemaker and mother of two children ages 4 and 2, is referred to psychiatric outpatient treatment by her general practitioner because of low mood, fatigue, and problems with memory and concentration. She separated from Robert, her children's father, a violent abusive man, 3 months ago, after 5 years of marriage. She describes a history of verbal and sometimes physical abuse beginning when she became pregnant with her first child, a son. The arguments would be over money or about his drinking, sometimes both. She finally decided to leave him when he held a gun to her head one night and threatened to kill her, the children, and himself.

Barbara is the younger of two sisters. She dropped out of high school in the 11th grade but later obtained her GED as well as a Certified Nurse's Assistant (CNA) license. She worked as a CNA for 3 years before her marriage to Robert and for 2 years thereafter until her son's birth. Before her marriage, she was living by herself, had an active social life composed of several friends from high school, and was close to her parents and saw them regularly. She had been popular in school, had been a cheerleader, and, until the 11th grade, had been a good student. Beginning in the 11th grade, she began dabbling in marijuana and drinking with friends over the weekend. As her grades declined, so did her interest in school, and she dropped out midway through the school year to work as a cashier at a local department store. A year later, she went back and got her GED and then her CNA license and worked steadily at a local nursing home until her delivery. She has no personal history of depression, no family history of mental illness or violence, and does not drink or use any illicit drugs.

In the 3 months since she left Robert, she has become increasingly depressed. She has no appetite and has lost 10 pounds from her already thin frame. She cries a lot, often wakes up at 3 a.m. and cannot go back to sleep, feels worthless, and has intermittent thoughts of death without any specific plan. On examination, she is pale, thin, and unkempt. She looks older than her age, speaks slowly, and appears depressed and slow in her movements. She has not gone out of the house or met any of her friends for more than a month and can barely make herself take care of her children. Her parents took her to her general practitioner, who found no evidence of any medical problems and referred her to the psychiatric clinic.

Barbara is clearly suffering from a *major depressive episode* (MDE) with five or more criteria symptoms of depressed mood, diminished interest or pleasure in almost all activities, decreased appetite or weight

a Cases are composites, not actual patients.

loss, insomnia, psychomotor retardation, feelings of worthlessness, problems with memory and concentration, and recurrent thoughts of death or dying. These symptoms are causing clinically significant distress or impairment in functioning and are not due to the direct effects of a substance or a medical condition. Barbara's MDE would be classified as a single episode, moderate to severe, without psychotic features, with melancholic features.

Stuck:

John, a 32-year-old man, is referred for medication management by his therapist. He has a master's degree in business administration from a prestigious business school and is currently working at a large firm as a mid-level manager. He complains about being "depressed" about "everything": his job, his girlfriend, and his future prospects. He has been in psychotherapy since starting college and has continued through graduate school until now. He complains of persistent feelings of pessimism and inferiority, low mood, and constantly ruminating about people who are "better than me." These feelings have been present (as far as he can remember) since he was about 15 or 16. He reports that therapy has helped him in the past but that "it never really goes away." John met his current girlfriend after starting his job in a new city. He was attracted to her, and a few months after they met, she moved in with him. Soon after this, they started fighting. He felt she was too critical, about his clothes, his job, and his friends; she found him moody, sullen, and withdrawn.

Recently, he has been having difficulties at work. He thinks his boss is unfair and self-centered, and he was recently passed over (twice) for a promotion. He feels this is unfair, although he admits that he performs his assignments half-heartedly, never does more than is absolutely required, and never takes any initiative. When he and his girlfriend socialize (which is rare), he feels people find him uninteresting and unimpressive. He is generally tired and dissatisfied with his life, his relationships, and his job and feels hopeless about the future.

John likely meets the criteria for a persistent depressive disorder. This updated category in the DSM-5 represents a consolidation of the two categories in the DSM-IV of chronic major depressive disorder and dysthymia.[5, 17] John has had a depressed mood most of the day on most days for more than 2 years. Along with a low mood, he also has symptoms of low energy or fatigue, low self-esteem, poor concentration and difficulty making decisions, and hopelessness. He has never had a manic or hypomanic episode, there are no symptoms of psychosis, and the symptoms cause clinically significant distress in functioning and are not due to the effects of a substance of abuse or a medical problem. In John's case, his illness presents with melancholic features, early onset (before age 21), mild or moderate, with pure dysthymic syndrome (i.e., the full criteria for MDE have not been met for the preceding 2 years).

The DSM-IV-TR

The fourth edition of the DSM was published in 1994. A major change from previous versions was the inclusion of a clinical significance criterion in almost half of all the categories, which required that symptoms cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning."

A "text revision" of the DSM-IV, known as the DSM-IV-TR,[37] was published in 2000. Most of the diagnostic categories and their criteria remained unchanged. The DSM-IV-TR was organized into a five-part axial system with each axis incorporating a specific axis of the condition under consideration: clinical disorders on Axis I and personality disorders and intellectual disabilities on Axis II. Axes III and IV covered medical, psychosocial, and environmental factors while Axis V provided a *Global Assessment of Functioning* numeric scale (from 1 to 100) to indicate how well or adaptively one is meeting various problems in day-to-day functioning.

The DSM-IV-TR included depressive illness in the section on mood disorders that also included illnesses with a cyclical pattern such as bipolar disorder and cyclothymia. The criteria for an MDE and MDD were similar to the later DSM-5, including specifiers for severity, presentation (melancholic, atypical, chronic), recurrence, etc.[17] A separate section within depressive disorders in the DSM-IV-TR was titled *Depressive Disorder*

NOS (Not Otherwise Specified) and included disorders with depressive symptoms that did not fulfill the criteria for MDE/MDD, dysthymic disorder, or adjustment disorder (symptoms following within 3 months of an identifiable stressor) or as part of an anxiety disorder NOS.[37] Examples of conditions included in the section *Depressive Disorder NOS* are premenstrual dysphoric disorder (mood symptoms occurring in the context of the menstrual cycle, minor depressive disorder in which fewer than the number of symptoms required to make a diagnosis of MDE/MDD were present for 2 weeks, and others).

The *Mood Disorders* section in the DSM-IV-TR also included manic, hypomanic, and mixed episodes of bipolar I and II disorder, cyclothymia, and bipolar disorder NOS, as well as mood disorders secondary to general medical conditions, medications, and substance abuse.[37]

The DSM-5

The DSM-5 was published on May 18, 2013, superseding the DSM-IV-TR. The first immediately noticeable change was in the name, in which the Roman numerals that denote the current edition, in use since the publication of the DSM-I in 1952, were dropped in favor of Arabic numerals. The newest DSM was named the DSM-5 (instead of the DSM-V). The APA maintained that this change was made to make it easier to disseminate the DSM's information in today's digital world and stated on the DSM website: "(today) Roman numerals are especially limiting. Research advances will continue to require text revisions to DSM and a TR designation, as was done with DSM-IV can only be done once. After DSM-5 is published in 2013, future changes to the manual's next complete revision will be signified as DSM-5.1, DSM-5.2 and so on."[38]

The DSM-5 has discarded the multiaxial system of diagnosis (formerly Axis I, Axis II, Axis III) and lists all disorders in Section II. The DSM-5 has replaced Axis IV with significant psychosocial and contextual features and dropped Axis V (Global Assessment of Functioning, known as GAF).[17]

The DSM-5 has attempted to remedy a common criticism of the DSM-IV and the DSM-IV-TR: Along with the categorical system of classification and diagnosis that could potentially fail to capture individual differences in disorder severity, dimensional severity ratings of the various diagnostic categories have been introduced and are meant to "serve as a bridge to new diagnostic approaches without disrupting current clinical practice or research."[17]

The new version discards the NOS categories of disorders and replaces them with other specified disorder and unspecified disorder. The first allows the clinician to specify the reason that the criteria for a specific disorder are not met or alternatively to forgo specification altogether. The DSM-5 has also done away with the DSM-IV-TR's Axis V, the GAF, because it was considered not clinically meaningful. In its place, WHO's *Disability Assessment Schedule* has been added to Section III (Emerging Measures and Models) under Assessment Measures, as a suggested, but not required, method for assessing functioning.

The new DSM has a number of important changes and updates on depressive disorders, including MDD. These changes include changes to the DSM-IV-TR diagnosis of dysthymia as well as the inclusion of two new disorders: disruptive mood regulation disorder and premenstrual dysphoric disorder.

Disruptive Mood Regulation Disorder:

This new diagnosis has been added specifically to address concerns about overdiagnosis and treatment of bipolar disorder in children and applies to "persistent irritability and frequent episodes of extreme behavioral dyscontrol… for children up to 10 years old."[17]

The diagnostic criteria include severe, recurrent temper outbursts (verbal or physical) that are inconsistent with developmental level, occur three or more times per week on average, during which the mood is predominantly angry or irritable. The symptoms need to have been present for 12 or more months with no symptom-free period for more than 3 months. The criteria need to be present in at least two of three settings (home, school, with peers) and be severe in at least one setting, and the diagnosis cannot be made before age 6 or after age 18. Other exclusions include the absence of any hypomanic or manic episodes, other illnesses such as autism spectrum disorder, posttraumatic stress disorder, etc., and the usual exclusion for medical conditions or substance abuse.

Premenstrual Dysphoric Disorder:

Premenstrual dysphoric disorder, listed as an appendix in the DSM-IV-TR,[37] is now recognized as a diagnosis in the DSM-5. Twelve-month prevalence rates of premenstrual dysphoric disorder have been estimated to be nearly 2%, **and the diagnostic criteria for the new disorder include symptoms that must be present in the final week before the onset of menses, start to improve within a few days of the onset of menses, and then become minimal in the week after menses. The symptoms include affective lability, anger or irritability, symptoms of depression, and symptoms of anxiety along with the following:** decreased interest and concentration, lethargy, appetite/sleep changes, feeling overwhelmed, and physical symptoms, such as bloating, weight gain, breast tenderness, or joint or muscle pain. As with all DSM diagnoses, the symptoms must cause clinically significant distress in functioning, and the usual exclusion criteria (cannot occur in the context of another disorder, e.g., MDD; cannot be due to the effects of a comorbid medical condition or substance abuse) apply. The DSM-5 recommends that 2 months of prospective symptoms ratings be carried out, including with appropriately validated scales, if necessary, before the diagnosis is made.[17]

Persistent Depressive Disorder (Dysthymia):

This is a new diagnosis in the DSM-5 and includes the DSM-IV diagnostic categories of chronic major depression and dysthymia.[17, 37] The core clinical features include depressed mood for at least 2 years on most days (the duration in children and adolescents can be 1 year, and the mood can be depressed or irritable) along with two or more symptoms of MDD (appetite and sleep changes, low energy, low self-esteem, poor concentration/indecision, and hopelessness). The symptoms must have been present for the specified duration with no symptom-free period for more than 2 months, and the criteria for MDD may be continuously present for 2 years. The illness period must not include any hypomanic or manic episodes and must not meet the criteria for cyclothymia, schizophrenia, persistent schizoaffective disorder, delusional disorder, or other specified or unspecified psychotic illness and must not be due to the effects of a medical condition or substance abuse. It is expected, due to the nature of the diagnostic criteria for persistent depressive disorder, that a very limited number of individuals will meet the criteria for MDE over the course of 2 years and those individuals should be given a diagnosis of MDD (and not persistent depressive disorder), although the DSM-5 allows a specifier of persistent MDE where the full criteria for MDE have been met throughout the preceding 2-year period. Other duration specifiers include persistent depressive disorder with pure dysthymic syndrome (where the criteria for MDE have never been present in the preceding 2-year period) and intermittent MDE, with and without a current episode. Morphological specifiers are also given, including with anxious distress, with mixed or melancholic features, with atypical features, etc. There are also specifiers for remission (full/partial), onset (early/late), and severity (mild/moderate/severe). According to the DSM-5, the 12-month prevalence of persistent depressive disorder in the US is 0.5% and for chronic MDD is 1.5%, and the social and occupational consequences of this condition can be as great or greater than MDD. Individuals with persistent depressive disorder are at higher risk for psychiatric comorbidity in general and for anxiety disorders and substance abuse in particular.

Major Depressive Disorder and the Bereavement Exclusion:

The core symptom criteria and the temporal duration (2 weeks) of MDE remain unchanged from the DSM-IV to the DSM-5.[5, 17] The presence of at least three manic symptoms (insufficient to meet the criteria for a manic episode) are now acknowledged in the specifier with mixed features that increases the likelihood of a bipolar spectrum illness; however, in the absence of a manic or hypomanic episode, the diagnosis of MDD is retained. Other specifiers include with anxious distress, with melancholic features, with atypical features, etc.

Recognizing the central importance of suicidal behavior in the assessment and treatment of depression, the clinician is given guidance on this subject in Section III under "Conditions for Further Study." There is a detailed section on assessment of suicidal thinking, plans, and the presence of other risk factors in order to make a detailed assessment and develop a comprehensive treatment plan.

The exclusion criterion for an MDE that had been applied to depressive symptoms lasting less than 2 months following the death of a loved one (i.e., the bereavement exclusion) has been removed in the DSM-5. This has been done for several reasons. Clinicians recognize that the 2-month duration of bereavement is atypical. The usual duration is more commonly 1–2 years. Second, it is generally acknowledged that bereavement is a severe psychosocial stressor that can precipitate MDE in a vulnerable individual within the stipulated 2-month period. Not diagnosing or treating MDE occurring in the context of bereavement poses the risk of further suffering and clinical deterioration and an increased risk for persistent complex bereavement disorder (discussed below). In addition, depressive symptoms associated with bereavement respond well to the same psychosocial and medication treatments as non-bereavement-related depression. In the criteria for MDD, a detailed footnote has replaced the more simplistic DSM-IV exclusion to aid clinicians in making the critical distinction between the symptoms characteristic of bereavement and those of an MDE, including (but not limited to) the following:

- **Feelings of emptiness and loss in grief in contrast to persistent depressed mood and the inability to anticipate happiness or pleasure. Grief dysphoria waxes and wanes ("pangs of grief") and generally subsides gradually over days to weeks.**
- **Grief is accompanied by persistent thoughts or reminders of the deceased, unlike MDE where the depressed mood is persistent and not specific to any thoughts or preoccupations.**
- **People who are grieving can still experience and share positive emotions and humor, unlike people with MDE. People with MDE are almost unfailingly self-critical with pessimistic ruminations, and feelings of worthlessness and self-loathing are common, unlike grief where self-esteem is generally preserved.**
- **Bereaved individuals may think about dying but usually in the context of their grief with wishes of joining the deceased. Patients with MDE feel worthless and undeserving of life and unable to cope with the pain of their depression and may plan suicide as a method of escape or relief from suffering.**

Persistent complex bereavement disorder (PCBD) is a newly proposed diagnosis included as an appendix under the "Conditions for Further Study" heading in Section III of the DSM-5. It lists symptoms that occur in response to the death of someone close to a person persisting for at least 12 months in adults and 6 months in children. In addition to symptoms typical of grief, such as yearning or longing for the deceased, sorrow, and preoccupation with the deceased or the circumstances of his or her death, symptoms are required from two clusters: reactive distress to the death, which may include bitterness or anger, numbness, excessive self-blame, etc., and social/identity disruption, such as wanting to die, feeling detached from others, feelings of meaninglessness or emptiness, etc. The symptoms should cause significant distress or difficulty functioning and be inconsistent with normal cultural or religious norms. There is a traumatic bereavement specifier for deaths due to suicide or homicide.

Conclusions

Depression is a common, highly debilitating illness that causes great morbidity, including medical morbidity. Depression is classified based on its morphologic features, but this approach has been criticized for various reasons. The pathophysiology of depression involves genetic, neuroanatomical, neurochemical, and immunological mechanisms that are still being investigated. The DSM-5 has made some key changes to the diagnostic criteria for various depressive illnesses. Disruptive mood regulation disorder in children and premenstrual dysphoric disorder for women have been added as new diagnoses. The diagnostic criteria for persistent depressive disorder (dysthymia) have been modified, and the bereavement exclusion has been removed from major depressive illness. The changes are meant to reflect the latest research and to align the DSM-5 more closely with the upcoming ICD-11. Clinicians must be aware of the changes in the DSM-5 as they pertain to depressive illness, keeping in mind the ubiquitous nature of these illnesses.

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L003359

Multiple-Choice Questions

61. What is the risk of completed suicide for patients with unipolar depression?

a. 5 times higher than that for the general population

b. 10 times higher than that for the general population

c. 20 times higher than that for the general population

d. 50 times higher than that for the general population

62. The causes of depression include:

a. genetic predisposition.

b. HPA Axis dysfunction.

c. immune system dysfunction.

d. all of the above

63. A patient comes to you with loss of appetite, sleep disturbances, crying spells, feelings of worthlessness and hopelessness, weight loss, and intermittent thoughts of death and dying. These symptoms have been present for a little over 1 month. The likely diagnosis is:

a. premenstrual dysphoric disorder.

b. major depressive episode.

c. schizophrenia.

d. persistent depressive disorder.

64. All of the following symptoms are present in bereavement, *except:*

a. feelings of emptiness and loss.

b. persistent reminders and thoughts of the deceased.

c. feelings of self-loathing and worthlessness.

d. ability to experience and share positive emotions and humor.

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Best Practices in CME

Depression: An Overview and Diagnostic Changes in DSM-5

By Ali M. Hashmi, MD; and Asim Shah, MD

ID#: L003359

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium of knowledge and daily practice.

CME Lesson Overview

In this lesson, we review the epidemiology and global disease burden of depression, briefly examine the types and their underlying neurobiology, and compare the changes in the diagnostic criteria for depression in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) to its predecessor (DSM-IV-TR).

Key Point 1: Prevalence of Depression

Depression is highly prevalent and highly debilitating both personally and socially. According to WHO, more than 350 million people of all ages suffer from *major depressive disorder* (MDD) globally, and about 20 million of those live in the US.

Key Point 2: Complexity of Depression

The neurobiology of depression involves a complex interplay among genetic, neurochemical, and immunological factors.

Key Point 3: DSM-5 Changes in Depression

The DSM-5 has added two new diagnostic categories of depressive illness: disruptive mood regulation disorder and premenstrual dysphoric disorder in women.

Key Point 4: Scope of Change from the DSM-IV-TR to the DSM-5

The diagnostic criteria for persistent depressive disorder (dysthymia) have been modified, and the bereavement exclusion has been removed from the criteria for the diagnosis of major depressive disorder to facilitate early diagnosis and treatment of a major depressive episode in the context of grief. Additional guidance is provided to clinicians on how to differentiate normal grief from major depressive episode.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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From Dementia to Neurocognitive Disorders: DSM-5 Changes

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

KEY WORDS: Dementia • Neurocognitive Disorders • Amnesia • Delirium • Cognitive Impairment

LEARNING OBJECTIVES: At the end of this lesson, clinicians should be able to: (1) summarize changes in the classification of neurocognitive disorders from the *Diagnostic & Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) to the fifth edition of the same manual (DSM-5), (2) appreciate how the new approach offers detailed descriptive and coding opportunities, (3) recognize the cognitive domains utilized in the DSM-5 for assessment and the differences between a major versus a mild neurocognitive disorder, (4) utilize the DSM-5 diagnostic format for neurocognitive disorders to advance from the main diagnosis to a potential causative etiology and then further refine the diagnosis in a probable versus possible manner according to the criteria, and (5) discuss challenges in the management and treatment of neurocognitive disorders and limitations in current treatment options.

LESSON ABSTRACT: This lesson addresses recent changes in the nomenclature and diagnostic classification in dementia/*neurocognitive disorders* (NCDs). It is often difficult for providers to determine where normal cognitive function ends and where decline begins, rendering dementia diagnoses difficult; it is similarly challenging to diagnose delirium. The recent transition from the DSM-IV-TR to the DSM-5 has brought about major changes in the way NCDs are classified. Thus, this lesson will address the new classification system. The DSM-5 classification allows 13 kinds of NCDs, and it is more aligned than its predecessors with the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) in that the DSM-5 allows more specific assignment of potential causality to observed symptoms. Major NCDs correspond to the entity previously known as dementia, and mild NCD has now been added to the DSM-5, corresponding roughly to the modest cognitive decline also known as minimal cognitive impairment.

COMPETENCY AREAS: NCDs (i.e., dementias) are challenging to treat and manage. Successful management often requires mastery of the following competencies, and this lesson will address relevant diagnostic and treatment directions: By bringing out global functional decline and increased dependency on other individuals, the disease calls on the provider to provide full patient-centered care, as every patient will have different goals in mind, different family and social support, and a different trajectory of the disease. Thus, treatment has to be customized. Additionally, as there is currently no cure for NCDs, interdisciplinary coordination with families, social work, nursing, and others, such as hospice, is necessary. Thus, interpersonal and communication skills will come into play repeatedly and often in complex ways. Last, as the knowledge base regarding NCDs continues to expand, employing evidence-based practice and updating medical knowledge are essential to optimize patient outcomes.

Introduction

Prevalence and Scope of the Problem:

Neurocognitive disorders (NCDs), the umbrella term for diseases characterized by impairment in cognition, are a growing problem for the developed world. Cognitive impairment can be present in other disorders (such as mood and psychotic disorders), but the differentiating feature for NCDs is the presence of cognitive impairment as a core feature of the clinical presentation. **NCDs include dementias, delirium, and disorders previously known as amnestic disorders.**

Delirium, disturbance in awareness, consciousness, and attention, can exist alone or superimposed on dementia or other disorders. Delirium is prevalent in a third of critically ill, hospitalized patients.[1] The development of delirium often leads to poor outcomes for patients. Florid, severe delirium is easy to identify, but a systematic lack of recognition has been noted, possibly because of the difficulty in ascertaining delirium diagnostically.[2]

Dementia prevalence is about 5%–7% worldwide in individuals around age 60, but prevalence increases drastically with increasing age, with a possibility of the risk doubling every 5 years. The most common type of dementia is Alzheimer's disease. In individuals around age 85, dementia prevalence reaches 20%, with up to 50% of individuals exhibiting symptoms of cognitive impairment.[3, 4]

The trajectory of cognitive decline varies according to the type of NCD. However, most NCDs lead, via insidious, progressive cognitive decline, to a loss of independence. Historically, dementia, previously known as senility, was thought to be unavoidable in older age, and has proven very difficult to treat despite advances in the field of medicine. Most management options focus on stabilizing patients, preserving dignity, and delaying the end of independence. Most individuals with NCDs end up requiring almost constant care or placement in skilled nursing facilities/nursing homes in late life.[5]

The *Global Deterioration Scale* (GDS)[6] can be used to follow the trajectory of dementia in seven stages; although initially meant to track decline in patients with Alzheimer's disease, the scale can be used for all NCDs. Predictable transitions that must be addressed in patients with NCDs include advanced planning for financial stability, healthcare considerations (power of attorney, medical decisions), driving cessation, supervision (including potential management of behavioral symptoms), changes in living circumstances (whether moving to a retirement community, a nursing home or other settings), and, last, end of life.

In this lesson, we will outline the main changes that pertain to NCDs from the DSM-IV-TR[7] to the DSM-5[8] and then discuss challenges in the management of associated behavioral symptoms.

Cognitive Disorders, Dementia, and Amnestic Disorders in the DSM-IV: A Picture in 2000

In the DSM-IV-TR,[7] NCDs, including delirium, dementia, and cognitive disorders, were included in one chapter, under the following unifying definition: "predominant disturbance is a clinically significant deficit in cognition that represents a change from a previous level of functioning."[7] Functional decline is a key feature to distinguish NCDs from neurodevelopmental disorders that interfere with childhood development. That distinction has been retained from the DSM-IV[9] to the DSM-5.[8]

Thus, delirium is characterized by changes in consciousness and cognition developing over short periods of time; dementia is characterized by multiple cognitive deficits, including impairment in memory, and is listed according to presumed etiology; and amnestic disorders are characterized by memory impairment in the absence of other significant cognitive impairment. The change from the *Diagnostic & Statistical Manual of Mental Disorders—3rd edition* (DSM-III)[10] to the DSM-IV was very significant for the field because the older terminology was "organic mental syndromes & disorders." Every change has evolved to reflect the expansion in the knowledge base related to NCDs. A common component among these disorders is the presence of a discernable, possibly *medical* etiology, though it could be due to substance use.

In delirium, the changes in consciousness are not accounted for by dementia, and the patient displays impairment in the ability to shift or sustain attention. Awareness of the surrounding environment is altered.

Disorientation may be noted and may fluctuate throughout the day. Delirium in the context of medical problems, severe illnesses, and increasing age is associated with increased mortality. Amnestic disorders vary widely, and are presumed to be due to medical conditions, substance use, or unknown etiology but retain the common component of memory loss; amnestic disorders are differentiated from dissociative disorders.

Dementia presentations share common symptomatology despite stemming from different etiologies. The DSM-IV allowed classification of dementia into dementia of the Alzheimer's type, vascular dementia, and dementias due to other medical conditions. These conditions include HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, and Creutzfeldt-Jakob disease. Additional categories include substance-induced persisting dementia, dementia due to multiple etiologies, and dementia not otherwise specified. The etiological distinction is still found in the DSM-5 and has been expanded upon. Memory impairment is the main feature. Delirium and dementia may be superimposed. Both may result from substance use as well (in an acute form for delirium and a persistent form for dementia). A major criticism of the DSM-IV classification was the lack of a category for cognitive symptoms that do not meet the diagnostic threshold for dementia, and subsequent classification changes address this issue.

Neurocognitive Disorders in the DSM-5: A More Structured Framework?

Neurocognitive disorders is the new term used in the DSM-5[8] and replaces the previous delirium, dementia, amnestic, and other cognitive disorders in the DSM-IV. The term neurocognitive disorders thus includes delirium, amnesia, and dementia. NCDs represent only *changes* from previously acquired functioning, as outlined above; divided into mild and major NCDs, the diseases are now diagnosed on a spectrum ranging from normal aging-related processes to pathological decline. The DSM-IV allowed diagnosis of dementia but did not include a provision for finer, more subtle changes that have been studied over the past two decades as minimal cognitive impairment. The gray zone between normal cognitive aging and dementia, including mild cognitive impairment, is now classified as a mild NCD.

Although potentially confusing, the transition from dementia to NCDs offers the opportunity for a more streamlined classification system that incorporates the vast advances in knowledge in the past few years. To complete an NCD diagnosis, impairment in six neurocognitive domains has to be evaluated: **(1) complex attention (sustained attention, divided attention, selective attention, processing speed); (2) executive function (planning, decision-making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility); (3) learning and memory (immediate memory, recent memory, very-long-term memory (autobiographical, semantic)) and implicit learning; (4) language (expressive and receptive); (5) perceptual-motor (visual perception, visuo-constructional, praxis and gnosis); and (6) social cognition (recognition of emotions, theory of mind).**

The patient may have impairment in one or more areas, and this will determine the type of NCD in question. For delirium, a required criterion is disturbance in attention, with an additional disturbance in cognition. Disorders known as amnestic in the DSM-IV will be under major NCDs due to another medical condition.

The term dementia will likely remain in use as a non-technical entity, much as the term addiction remains despite the advent of substance use disorders. Neurocognitive disorder is, nevertheless, a broader term than dementia, and the diagnosis includes the NCD etiology; etiological subtypes include NCD due to Alzheimer's disease, vascular NCD, NCD with Lewy bodies, NCD due to Parkinson's disease, frontotemporal NCD, NCD due to traumatic brain injury, NCD due to HIV infection, substance/medication-induced NCD, NCD due to Huntington's disease, NCD due to prion disease, NCD due to another medical condition, NCD due to multiple etiologies, and unspecified NCD. Compared to the DSM-IV, the DSM-5 allows each category to be diagnosed independently, instead of being linked to an "other" medical etiology.

Once a diagnosis of an NCD is made, the next diagnostic step is to determine the level of impairment associated with this diagnosis, further classifying the NCD into mild versus major. The differentiation between a mild and major NCD reflects the level of severity of the cognitive, behavioral, and functional symptoms. A mild NCD means that objective deficits are present that exceed findings related to normal aging. A major versus mild NCD distinction can help guide treatment planning. The overarching goal of treatment is the prevention of progression from a mild to major NCD.

The main NCD diagnoses and their characteristics are detailed below.

Delirium:

As outlined above, the major descriptors of delirium have not changed much from the DSM-IV to the DSM-5, but subtyping has been refined. The current specifiers are more aligned with the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) terminology, providing more clarity and ease of use across diagnostic frameworks. Specifiers allow the clinician to indicate the suspected etiology. The specifiers allowed for delirium include substance intoxication delirium, substance withdrawal delirium, medication-induced delirium, delirium due to multiple etiologies, and delirium due to another medical condition. Additionally, the clinician can specify whether the delirium is acute, persistent, hyperactive, hypoactive, or with a mixed level of activity. The clinical presentation in delirium can shift rapidly, and the specifiers are linked to the predominant symptomatology seen at the time of diagnosis.

Clinically, the essential features and criteria of delirium remain as such. Developing over hours to days, delirium involves disturbances in attention and awareness and an additional disturbance in cognition. An etiology is suspected (and coded as such). Delirium is often associated with sleep-wake cycle disturbances, emotional disturbances (such as anxiety and rapid switches in mood), behavioral disturbances, and sometimes hallucinations. However, none of these disturbances constitute core diagnostic symptoms. Hallucinations tend to be visual, especially in the context of alcohol withdrawal delirium.

The main differential diagnosis for delirium remains another NCD, although the possibilities range from mood disorders to psychosis, substance intoxication or withdrawal, and acute stress disorder.

In the case of delirium that meets sub-threshold clinical criteria, the clinician may use other specified delirium, or attenuated delirium syndrome. Last, if the clinician does not feel ready to assign a potential etiology to the clinical picture that nevertheless meets criteria for delirium, the diagnosis of unspecified delirium can be assigned.

Major Versus Mild Neurocognitive Disorders:

Thirteen categories of major NCDs are allowed in the DSM-5 as outlined above. **All major NCDs share the main criteria of (1) significant cognitive decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition) with (2) performance impairment and (3) interference with everyday activity. Loss of independence is emphasized in the DSM-5 criteria,** as well as the need to have a quantified clinical assessment or standardized neuropsychological testing, which remains the gold standard for diagnosis.

Mild NCDs represent the transitional stage between normal aging and a major NCD diagnosis. Upon diagnosing a patient, the clinician needs to remember that major and mild NCDs exist on a spectrum. The DSM-5 criteria describe the cognitive decline in mild NCDs as modest. An individual with a mild NCD may have difficulty achieving tasks related to everyday life, may have to use compensatory strategies (e.g., use reminders, ask for help at times, need more time for completion), or give up certain activities. Obtaining collateral information about how the patient is functioning from family or friends is crucial to clarify symptom severity, as the individual may be unable to report the decline accurately once involved in a cycle of compensatory measures.

In line with the streamlining of diagnosis for NCDs, the diagnosis of a mild NCD has the same potential 13 specifiers as a major NCD (Alzheimer's disease, vascular disease, Lewy bodies disease, Parkinson's disease, fronto-temporal lobar degeneration, traumatic brain injury, HIV infection, substance/medication use, Huntington's

disease, prion disease, another medical condition, multiple etiologies, and unspecified).

NCDs Due to Alzheimer's Disease:

NCD due to Alzheimer's disease is diagnosed when there is an insidious onset and a gradual progression of impairment in cognitive domains. The clinical picture in the NCD due to Alzheimer's disease tends to start with memory problems, before impairment in other areas becomes obvious. One domain impairment leads to a mild NCD, whereas the impairment of two domains is required for a major NCD. NCD due to Alzheimer's disease can further be classified as causatively probable or possible based on the clinical picture and genetic background. For a probable NCD, evidence of genetic mutation (testing or family history) or meeting three of three criteria is necessary. See the figure for details.

NCD due to Alzheimer's disease was described by Aloysius Alzheimer, inspired by the case of a 50-year-old woman in his clinical practice. He described the case in 1906.[11] Silver stain was used to reveal the neurofibrillary tangles, now known as one of the landmark findings in NCD due to Alzheimer's disease. **The disease terminology has become synonymous with dementia globally, as NCD due to Alzheimer's disease is the most common form of dementia.** Risk factors for developing NCD due to Alzheimer's disease are age and genetic susceptibility to an apolipoprotein E4 polymorphism in homozygous individuals.[12, 13] Autosomal dominant cases with early onset can be due to mutation in *amyloid precursor protein* (APP), *presenilin 1* (PSEN1),[14] or *presenilin 2* (PSEN2).[15] These genetic mutations are considered causative.[14]

No racial differences between African Americans and Caucasians have been found in terms of prevalence when controlling for education, gender, and apolipoprotein E genotype,[13] though earlier data suggested a slight preponderance of dementia prevalence among individuals of African American descent.

Pathognomonic pathological findings include[17, 18] neuritic plaques (amyloid proteins), neurofibrillary tangles (tau proteins mostly), and cortical atrophy. However, they can be confirmed at autopsy unless functional imaging is conducted.

Treatment of NCD due to Alzheimer's disease is a field of intense study. The targets for treatment remain cholinergic function and glutamatergic tone via N-methyl-D-aspartate receptors, but research into other areas is promising.[3, 19-20] Thus far, pharmacological agents including *donepezil* (Aricept), *rivastigmine* (Exelon), *galantamine* (Razadyne), which are cholinesterase inhibitors, and *memantine* (Namenda), NMDA receptor antagonist, have been approved for treatment.

Frontotemporal NCD:

Frontotemporal dementia is the second most prevalent type of NCD according to certain sources,[21] though this NCD may be ranked closely with vascular NCD. **Frontotemporal NCD is often noted to start in patients of younger age, less than 65.**

Once the individual has met the criteria for a mild or major NCD, frontotemporal NCD is suspected when a behavioral or language variant is present. Unlike NCD due to Alzheimer's disease, memory and learning may be relatively spared in early stages of the disease, sometimes leading to erroneous diagnoses of primary psychiatric disorders.[22, 23] **Behavioral variant criteria include behavioral disinhibition; apathy/inertia; loss of sympathy/empathy; perseverative, stereotyped or compulsive/ritualistic behaviors; hyperorality; and dietary changes. Language variant criteria focus on decline in language ability, ranging from speech production to word comprehension.[22]** Three varieties of language impairment are defined but are not coded (semantic, agrammatic/nonfluent, and logopenic).

Only one variant is needed for diagnosis (behavioral versus language), although a clinical mixture of both is often present. A probable frontotemporal diagnosis is made if there is a family history, genetic testing (mutations in microtubules-associated protein tau), or evidence from neuroimaging of clinically significant, disproportionate frontal or temporal lobe involvement.[24]

No effective pharmacological treatment is known for frontotemporal NCD. Treatment with cholinesterase inhibitors and memantine has not proven helpful. Selective serotonin reuptake inhibitors and other antidepressants may be helpful in controlling behavioral manifestations. Management of comorbid behavioral symptoms is emphasized.[25]

NCD with Lewy Bodies:

NCD with Lewy bodies (NCDLB), previously known as dementia with Lewy bodies, is a complex disorder

that encompasses cognitive impairment as well as sleep manifestations, visual hallucinations, and even delusions. Parkinsonian-like motor symptoms occur after cognitive decline. The clinical picture tends to fluctuate, and diagnosis is challenging. Lewy bodies are typically in the cortex. NCDLB is a synucleipathy:[26] The protein *alpha-synuclein* (α-Syn) accumulates within neurons and glial cells, causing degeneration and impaired connectivity (for an excellent review, see Valera et al.[27]), and the propagation of alpha-synuclein is toxic to neuronal cells.

To make a NCDLB diagnosis, the DSM-5 requires a combination of core diagnostic features and suggestive diagnostic features. Core diagnostic features include: (1) fluctuating cognition with pronounced variation in attention/alertness, (2) recurrent well-formed, detailed visual hallucinations, and (3) spontaneous features of parkinsonism.

Suggestive features include meeting criteria of rapid eye movement sleep behavior disorder or severe neuroleptic sensitivity.

Clinically, assessment must include a heightened awareness of risk of falls, syncope, and overall manifestation of autonomic dysfunction. Delusions and delusional misidentification can be present in individuals with NCDLB. However, because of sensitivity to neuroleptics, treatment must be undertaken with caution. No fully effective treatment is available for NCDLB.

Vascular Neurocognitive Disorder:

Vascular NCD is a heterogeneous disease that can result from small or large vessel disease. Vascular NCD is not the same as post-stroke cognitive impairment, which is worse right after the stroke, and may improve with time. Vascular NCD, in contrast, is a chronic illness. Contrary to the NCD subtypes mentioned previously, the course of vascular NCD can be noted to have periods of stability followed by abrupt declines, coinciding with new cerebrovascular events. Vascular NCD is common, possibly as common as NCD due to Lewy bodies disease,[28] though prevalence statistics vary according to the cited sources and sampled populations.

According to the DSM-5, vascular NCD is diagnosed when the onset of the cognitive deficits is temporally related to cerebrovascular events; the second requirement is that two areas of prominent cognitive decline in complex attention (including processing speed) and frontal-executive function. To further assign causality and diagnose probable vascular NCD, one of the following three criteria must be met: "1. neuroimaging evidence of parenchymal injury attributed to cerebrovascular disease consistent with the clinical picture, 2. Temporal relation of cognitive deficits to one or more documented cerebrovascular events or 3. Both clinical and genetic evidence of cerebrovascular disease is present."[9]

Treatment is focused on behavioral manifestation management. No primary treatment exists for vascular NCD.

NCD Due to Parkinson's Disease:

The hallmark of NCD due to Parkinson's disease is the gradual, insidious development of cognitive deficits after the development of Parkinson's disease. Parkinson's disease's prevalence increases with age.[29] Up to 75% of individuals with advanced Parkinson's disease develop an NCD; the disease is characterized by bradykinesia, tremor, rigidity, and impaired balance. Pathophysiology was thought to be mostly linked to dopaminergic dysfunction,[30] but a more modern understanding of the disease points to Parkinson's being an α-synucleinopathy, with axonal degeneration, and potential mitochondrial involvement.[31-33] The dopaminergic dysfunction is still prominent and may be responsible not only for motor symptoms but also for the nonmotor, neurocognitive issues faced in Parkinson's disease. Anxiety, depression, sleep disturbances, and impulsivity issues are very common in Parkinson's disease.[34]

As with other NCD categories in the DSM-5, the patient has to first meet the criteria for a mild or major NCD; the disease is then classified as either probably or possibly due to Parkinson's disease, following DSM-5 classification schemes. Careful history-taking allows the clinician to establish a timeline. However, medical comorbidities may cloud the causality issue, and in the case of intervening diagnoses that could explain the neurocognitive findings at hand, a diagnosis of NCD possibly due to Parkinson's disease will then be made.

The main differential diagnosis for NCD due to Parkinson's disease is other NCDs, ranging from vascular

NCD to NCDLB. When attempting to clarify the diagnosis, and given the motor abnormalities associated with Parkinson's disease, testing that emphasizes cognitive function should be preferentially used. In a comparison of individuals with NCD due to Parkinson's disease versus a group afflicted with NCDLB, the pattern of cognitive deficits on the *Mini-Mental Status Examination* can reliably distinguish the etiology of the NCD,[35] with NCD due to Parkinson's disease expressed with more motor dysfunction.[36] Dopamine transporter scans may distinguish Parkinson's disease from other NCD etiologies.[37, 38]

NCD Due to Traumatic Brain Injury:

In addition to the temporal association of a brain injury with cognitive deficits, one of the following must be present for a diagnosis of NCD due to traumatic brain injury: loss of consciousness, posttraumatic amnesia, disorientation and confusion, and neurological signs. Temporal association is important and constitutes criterion C in the DSM-5: thus, the cognitive deficits have to occur after the traumatic injury.

The clinical picture in NCD due to traumatic brain injury is very heterogeneous given the number of possibilities that can lead to this condition. Additionally, the presence of physical issues such as seizures add a complicating dimension to the assessment. Irritability, personality changes, and emotional disturbances are frequently present, and are the main targets of management.

Other NCDs, such as NCD due to HIV infection, substance/medication-induced NCD, NCD due to Huntington's disease, and NCD due to prion disease, follow the same diagnostic scheme outlined. The individual must first meet the criteria for a major or mild NCD. Evidence of a causative link (e.g., an HIV diagnosis, evidence of prior disease) is the next step in making the diagnosis more specific.

Behavioral Manifestations in NCD:

One of the major advances in the field of NCD study is the current recognition that neurobehavioral symptomatology represents an integral part of the development of neurocognitive decline. Many individuals are diagnosed with depression or anxiety before they receive a correct NCD diagnosis. From a financial standpoint, the management of neuropsychiatric disturbances in dementia accounts for 33% of the global cost of dementia and is associated with low income and unemployment in caregivers.[39]

The following symptoms must be carefully assessed in suspected NCD:[40-42] psychotic symptoms, apathy, agitation, mood disturbances, anxiety/depression, and sleep disturbances. The clinician treating patients with NCDs will undoubtedly encounter all these symptoms at one point or another during the treatment course. Behavioral symptoms do not point toward particular NCD subtypes in a pathognomonic way, although certain patterns are recognized, as outlined in the specific sections.

That being said, two challenges face effective management of behavioral symptoms in NCDs. The first is that presentations vary across the spectrum of healthcare settings (please see cases 1 to 3 for illustrative examples). The second is that treatment is mainly symptomatic, but patients with NCD may have difficulty with various pharmacological modalities: Increased mortality with antipsychotic use in dementia is a classic example of the delicate balancing act required from the treating clinician. Other examples include the risk of disinhibition or increasing fall risks with sedatives commonly prescribed off-label to control behavioral issues in NCD, and the high prevalence of poly-pharmacy in the elderly.

In general, the clinician should focus on behavioral approaches prior to initiating medications. Modifiable factors that can potentially worsen behavioral symptoms can include deteriorating physical health, pain, insomnia, changes in caregivers or in the home environment, etc. For depression, several approaches can be used, including *electroconvulsive therapy* (ECT), pharmacotherapy, and psychosocial modalities. Psychosocial interventions are the first-line treatment and should be tried for at least 2–4 weeks.[43, 44] For sleep issues, non-pharmacological treatments include sleep hygiene, light therapy, and exercise. Pharmacological treatment should be considered only after non-pharmacological interventions have failed, and after the potential benefits and side effects have been pondered carefully. If used, pharmacological treatment should be used only for a short time because few data exist on their long-term safety and use in cognitively impaired individuals.[45]

Case Studies in NCD:

The following cases illustrate how varied the clinical presentation of individuals with NCDs can be.

Case 1: NCD in the Emergency Setting

Mr. BW is an African-American, 59-year-old male who is evaluated in the emergency department for the chief complaint of "altered mental state." The patient's chart indicates a prior remote history of depression, hypertension, and alcohol use. He has not been seen in your health system for more than 10 years, and no collateral information is available today. The patient was picked up by the police as he was wandering in the park close to your facility. He looked confused and was brought in for evaluation.

On assessment, the patient is oriented to self and says he is in a hospital, which he cannot name. He is oriented to the month only, not the year or day. He cannot give a history of the events preceding his presentation. He asks for help with his living situation and medications, but his statements are vague and contradictory. The nursing staff reports the patient appears to have visual hallucinations and is picking invisible items off his sheets, saying he has to clean up for Christmas. Upon assessment, he is initially calm, cooperative, and pleasant, but then reports to you he is being "followed…tracked" and says, "*I'm a dead man, do you see them*?" He then jumps out of bed and starts folding the sheet while mumbling.

Vital signs reveal mild tachycardia, with a heart rate of about 90 beats/minute, but are otherwise unremarkable. A complete blood count and a basic metabolic panel are unremarkable. However, the patient has mild transaminase elevation and an ammonia level of 35, the upper range being 32.

In the first case, which takes place in the emergency department setting (typically devoid of an adequate background history), the clinician can diagnose delirium, but without the ability to ascertain an organic cause. The waxing and waning levels of awareness and the presence of visual hallucinations aid in making a diagnosis of delirium.

Case 2: NCD in the Outpatient Setting:

Today, you are seeing Ms. Robinson in the clinic. A 73-year-old petite woman of Caucasian descent, she presents with her daughter and her grandson who brought a copy of her medical records. The patient is seen for an outpatient evaluation of memory deficits and "personality changes." The visit was initiated by her family, who reported that the patient has been forgetful, got lost on several occasions while driving to visit her daughter, and has been accusing people of stealing items from her home. This has prompted her to change all the locks in the home, and she has fired four successive cleaning staff that her family had hired for domestic assistance. The patient found the items she had claimed had been stolen, and she tells you in great detail how she believes the staff brought the items back and, in the process, broke into her home. She calmly reminds you she's "not crazy."

Ms. Robinson denies any medical problems except for diabetes that she controls with diet. Her family is concerned that she is no longer cooking elaborate meals as she used to. Depressive symptoms were noted 5 years ago when her husband died, but she seemed to recover and moved to a smaller home. The memory and behavior changes started about 2 years ago. The patient has been resistant to get an evaluation, accusing her family of interfering in her private business. Her family is worried because the patient's mother had dementia and was in a nursing home toward the end of her life.

The second case describes the typical gradual insidious onset of an NCD, likely of Alzheimer's disease, and the challenges that such a diagnosis brings, including family strain and patients rejecting the possibility of having an NCD. The case is straightforward, and the presence of a family history helps the clinician form a strong differential diagnosis. However, confirmatory testing, whether clinical or imaging, is highly recommended to ascertain the diagnosis.

Case 3: NCD in the Chronic Care Setting

Your patient is an 80-year-old man with a history of NCD possibly due to vascular disease who was recently placed in a skilled nursing facility. You are consulted to weigh in on severe insomnia, as well as behavioral issues that occur almost every evening.

The patient is a retired school teacher who moved to the facility about a month ago. He has a history of hypertension, several mini strokes, and diabetes; he had to abandon his independent retirement community living after a hip fracture. He is friendly to staff during the day, follows the home's rules, and eats independently. He has started to ambulate independently as well. He plays bingo marginally, seeming to enjoy the process more than the actual game, and walks in the yard during the day for 5- to 10-minute stretches. His baseline clinical status is described as forgetful, and he has not been driving for at least 5 years. He has required assistance with meal preparation for about 3 years.

The symptoms you are seeing this patient for were described by the staff as different from his usual forgetfulness. Around 6 p.m., he becomes confused, sometimes calls for absent family members, and once was found trying to open the balcony door. He wanted to jump.

In the third case, we describe delirium superimposed on a preexisting major NCD. The patient has several medical issues that complicate care. Sun-downing is suspected, with worsening in awareness and consciousness in the evening.

Conclusions

NCDs represent a tremendous societal burden. With increasing age expectancy, more individuals live to experience cognitive decline and the associated loss of independence. Previous challenges in the NCD field included the fact that many diagnoses could be verified only postmortem, on autopsy; with the advent of more advanced neuroimaging, some of these barriers may be part of the past soon. Additionally, and although there are no effective treatments for NCDs yet, more targeted approaches are very promising. The DSM-5 tries to incorporate the recent exponentially increasing information and knowledge in the NCD field. Thus, the DSM-5 classification, allowing for more precise assignment of causality to NCD diagnoses, stratification into a major versus mild NCD, and then assignment of a probable versus possible etiology, provides a logical, structured framework that clinicians will be able to utilize for all NCDs.

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L003360

Multiple-Choice Questions

65. According to the DSM-5, a neurocognitive disorder can be accompanied by impairment in the following domains, *except*:

A. complex attention.

B. executive function.

C. social cognition.

D. appetite.

66. The most common etiology of neurocognitive disorders is:

A. Alzheimer's disease.

B. Huntington's disease.

C. vascular disease.

D. frontotemporal pathology.

67. A 57-year-old man with no past psychiatric history presents to your clinic for evaluation of symptoms of depression, hallucinations, and anxiety. The patient denies a family history of neurocognitive disorders and has no personal medical history. Until 2 years ago, he was employed on a full-time basis but had several mood outbursts that cost him his job. His wife complains he has developed an appetite and has gained "a lot of weight." She also complains he is no longer able to "tell her sweet things" "like he's lost his language talents." The patient is most likely suffering from:

A. an NCD due to Alzheimer's disease.

B. an NCD due to Huntington's disease.

C. an NCD due to vascular disease.

D. frontotemporal NCD.

68. Which of the following statements is false?

A. Neurocognitive disorders include dementias, delirium, and the entity previously known as amnestic disorders.

B. Dissociative disorders are a neurocognitive disorder according to the DSM-5 classification.

C. The DSM-5 allows the classification of neurocognitive disorders into major versus mild based on the severity of symptoms and impairment.

D. The presence of a mild neurocognitive disorder does not necessarily lead to loss of independence.

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Best Practices in CME

From Dementia to Neurocognitive Disorders: DSM-5 Changes

By Nidal Moukaddam, MD, PhD, and Asim Shah, MD

ID#: L003360

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium of knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to psychiatrists, family physicians, and other providers who take care of individuals with cognitive deficits and who require information on the classification of *neurocognitive disorders* (NCDs) in the new DSM-5.

Key Point 1: Main Scope of Change from the DSM-IV-TR to the DSM-5

The DSM-5 classification includes delirium and entities previously known as dementia but now called NCDs. Amnestic disorders no longer have a category of their own as they did in the DSM-IV. The DSM-5 allows better alignment with the way diagnoses are made in the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10).

Key Point 2: Mild Neurocognitive Disorder Has Been Added to the DSM-5

The DSM-5 allows the diagnosis of mild NCDs, which is the equivalent of the entity previously known as minimal cognitive impairment. At this stage, individuals have cognitive deficits but are usually able to retain their independence.

Key Point 3: The DSM-5 Follows the Same Classification System for All NCDs

The DSM-5 allows 13 categories for NCDs and allows the clinician to point to a potential etiology for the observed deficits. Once the individual meets the criteria for a major or mild NCD, he or she can then be diagnosed with an NCD due to a particular etiology, and the latter can be specified further as possible or probable.

Key Point 4: Delirium Diagnosis Is More Specific in the DSM-5

The diagnostic criteria for delirium have not changed much from the DSM-IV to the DSM-5. However, the diagnosis can have specifiers that aid in assigning the etiology of the observed mental state alteration and describing it as hyperactive, mixed, etc.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Cognitive Impairments in Alcohol-Dependent Subjects

Florent Bernardin, Anne Maheut-Bosser, and François Paille

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

KEY WORDS: Alcohol-dependence • Brain Atrophy • Cognitive Impairments • Inhibition • Working Memory • Implicit Cognition • Cognitive Remediation Therapy

LEARNING OBJECTIVES: This lesson reviews how excessive alcohol consumption induces cognitive impairments mainly affecting executive functions, how cognitive impairment can be improved with cessation of alcohol consumption, and lastly, how cognition can be improved by implementing cognitive remediation therapy which has been shown to increase cognition and other domains.

LESSON ABSTRACT: Chronic excessive alcohol consumption induces cognitive impairments mainly affecting executive functions, episodic memory, and visuospatial capacities related to multiple brain lesions. These cognitive impairments not only determine everyday management of these patients, but also impact on the efficacy of management and may compromise the abstinence prognosis. Maintenance of lasting abstinence is associated with cognitive recovery in these patients, but some impairments may persist and interfere with the good conduct and the efficacy of management. It therefore appears essential to clearly define neuropsychological management designed to identify and evaluate the type and severity of alcohol-related cognitive impairments. It is also essential to develop cognitive remediation therapy so that the patient can fully benefit from the management proposed in addiction medicine units.

COMPETENCY AREAS: This lesson reviews the correlation of cognitive impairment and chronic alcohol consumption in patients. Clinicians will be better informed to assess and address cognitive impairment in treatment by considering cognitive remediation therapy.

Introduction

Alcoholism causes a multitude of social and health problems with negative impact on quality of life and secondary costs to society.[1–3] Evidence suggests that numerous determinants such as environmental, individual, and genetic factors could favor evolution toward alcohol-dependence. These factors may also interact with each other. Among environmental factors, quality of the neighborhood[4] or socio-economic factors (e.g., lower educational level, employment status)[5, 6] for example may increase risks of alcohol abuse. **Individual and psychological characteristics including comorbid psychiatric disorders,[7, 8] early life stress exposure,[9] or impulsivity[10] are also risk-factors associated with chronic alcohol consumption.** In addition, family, twin, and adoption studies have highlighted that genetic factors play an important role in the pathogenesis of alcohol-dependence.[11-13] Heritability of alcohol-dependence is estimated between 50% and 80%[14] and is considered as a complex polygenic phenotype. In the same way, recent studies have examined cognitive endophenotype in alcoholism. They have shown that non-alcoholic relatives of alcohol-dependent individuals performed worse on cognitive tasks (specifically executive functions) and presented greater impulsiveness compared to control [e.g., Ref. (15)].

From a neurobiological perspective, alcohol-dependence is a chronic disorder, which implies the dopaminergic system. As seen in other drug abuses, alcohol consumption acutely stimulates *dopamine* (DA) release from the major terminal area of the mesolimbic DA system, *nucleus accumbens* (NAC). Enhanced DA transmission in the NAC plays a critical role in the positive rewarding aspects of drugs abuses and the initiation of the addictive process. Chronic administration is associated with functional alterations of this important part of the brain reward system. Globally, dysregulation of the dopaminergic system caused by chronic alcohol consumption produces drug dependence reinforcement and is most likely involved in the development of drug addiction.[16-18]

The harmful effects of chronic alcohol consumption on the brain and cognitive functioning have been well described in the literature over recent decades.[19] Cognitive impairments observed in alcohol-dependent patients not presenting any other neurological complications are increasingly becoming the focus of attention of addiction medicine professionals due to their impact on management, as, according to various studies, between 50% and 80% of these patients present impaired cognitive function.[20, 21] These impairments are moderate to severe but usually remain undiagnosed when they are not specifically investigated. However, detailed neuropsychological assessment or screening of these cognitive impairments appears to be fundamental to optimally adapt patient management strategies.

Alcohol-Related Cognitive Impairments

Neuroanatomical alterations can account for cognitive impairments affecting various functions, primarily executive functions.[22] Fifty to 80% of patients present alterations of cognitive functions that probably impact on their management. However, there is a marked inter-individual variability of the nature and severity of these impairments.

Ihara et al.[23] defined four profiles in these patients: (1) no cognitive impairment, (2) isolated executive deficits with no impairment of memory and global cognitive efficiency, (3) modified dysexecutive syndrome with memory impairments and preservation of global cognitive efficiency, and[4] global impairment (executive, memory, and global cognitive efficiency). **More specifically, the dysexecutive syndrome can affect various processes such as working memory,[24] mental flexibility,[25] divided attention,[26] decision-making,[27, 28] or problem-solving.[29]** Disorders of prepotent response inhibition play a predominant role in addiction medicine to the point that alcohol-dependence has been described as a "disinhibitory disorder."[8]

The characteristic profile of alteration of episodic memory in alcohol-dependent patients comprises limited learning capacities, impairments of encoding, and recollection processes, difficulties recalling the temporo-spatial context and deficits of autonoetic consciousness, while information storage is preserved.[25, 30] Alteration of executive functions, particularly disorders of inhibition, flexibility, or dual-task coordination also constitute predictive factors of memory impairment.[25, 30] In contrast, apart from obvious deficits (i.e., related to dysexecutive syndrome), there is also probably a genuine impairment of episodic memory likely due to the hippocampal atrophy observed in these patients.[25]

Finally, visuospatial functions are also predominantly affected, as several studies have demonstrated impaired performances on visuospatial processing, memory and visual learning, visuospatial organization, and visuoconstruction tasks.[31, 32]

Three main hypotheses have been proposed in the literature to account for the characteristic cognitive profile observed in alcohol-dependent patients [see Ref. (31) for a detailed review of these hypotheses].

The first hypothesis is based on the pervasiveness and impaired recovery after withdrawal of visuospatial cognitive functions that are attributed to the non-dominant hemisphere. The right hemisphere would therefore be more susceptible to the neurotoxic effects of alcohol.[32] However, this postulate has been questioned by contradictory results.[31] The second hypothesis proposes that the increased susceptibility of frontal structures would account for the cognitive profile dominated by executive deficits.[33] However, this hypothesis also appears to be too restrictive, as other cerebral structures are also involved.[34] The third hypothesis, based on neuroanatomical and neuropsychological data, reconciles the previous two hypotheses by postulating the existence of global brain damage.[35] In their meta-analysis of neuroanatomical data, the authors emphasized not only the existence of right hemisphere and frontal lobe lesions, but also lesions affecting other cerebral regions (medial temporal, subcortical, and cerebellar atrophy). The neuropsychological functional deficits observed in these patients also concern several cognitive functions in both verbal and visual modalities, which constitutes an additional argument in favor of the global brain damage hypothesis.

Anatomical Lesions

Chronic excessive alcohol consumption induces global brain atrophy characterized by reduction of brain volume and enlargement of the ventricles and sulci.[36] The severity of brain damage depends on various factors such as the extent of alcohol consumption, age, gender, and neurological or psychiatric comorbidities.[31] **The most susceptible brain structures are the neocortex in the frontal lobes, the limbic system, and the cerebellum.[37] Reduction of gray matter preferentially involves frontoparietal regions, while reduction of white matter tends to be more diffuse.[22]**

More precisely, Kril et al.[38] estimated that chronic alcohol consumption induced about 15%–23% loss of neuronal density in the frontal regions. This result is concordant with those of a more recent study, which demonstrated a 20% reduction of the gray matter volume in the dorsolateral prefrontal cortex.[22] Pfefferbaum et al.[39] showed that aging brain is more sensitive to the deleterious effects of excessive alcohol consumption. This study indicates that the profile of brain damage in the frontal lobes varies according to the patient's age even after accounting for the effects of normal aging and regardless of amounts of lifetime consumption of alcohol or duration of illness. Therefore, these results indicate an increased susceptibility of the brain in the elderly according to the model of alcohol-related premature aging of the brain.[40] Furthermore, many studies have also demonstrated functional changes with a reduction of glucose metabolism or cerebral blood flow in prefrontal regions, particularly in the medial temporal region.[37]

Alcohol-related brain damage also concerns the limbic system and particularly the hippocampus, regions involved in episodic memory.[41-44] The hypothalamus and mammillary bodies are also particularly susceptible to chronic excessive alcohol consumption, especially when it is accompanied by vitamin deficiencies as in Wernicke's encephalopathy or Korsakoff's syndrome.

Finally, the cerebellum is also affected in these patients, with a reduction of the white matter volume in the vermis and cerebellar hemispheres.[40] A study of the connections between the cerebellum and frontal regions via the pons and thalamus also demonstrated alteration of the frontocerebellar circuit.[34]

Detection and Diagnosis

In this context, the detection of cognitive impairments in alcohol-dependent patients is therefore essential and should be systematic. **The *Montreal Cognitive Assessment* (MoCA) Test appears to be the most appropriate screening test for detection of cognitive impairments in these patients,[45] as this tool is more sensitive than the *Mini Mental State Examination* (MMSE) for mild-to-moderate cognitive impairments.[46]** The MoCA Test can be performed by medical students, medical doctors, or certified neuropsychologist. Detection of cognitive impairments can then lead to referral of the patient for neuropsychological diagnostic assessment performed by a clinical neuropsychologist. Neuropsychological

assessments can last 2–3 hours and are designed to demonstrate preservation or impairment of the most susceptible cognitive functions in this population. Clinical neuropsychologists have at their disposal a battery of tests to evaluate several cognitive domains such as memory (e.g., *California Verbal Learning* test and *Doors and People* test), executive functions (e.g., *Trail Making Test* part B and *Wisconsin Card Sorting Test*, the *Stroop Color Word* test, and the *Letter Fluency Test*), working memory (*Digit Span and Letter-Number Sequencing* test), or processing speed *(Digit Symbol-Coding*).

In the alcohol-dependent population, the most susceptible executive processes to be evaluated are working memory, mental flexibility, inhibition, processing speed, concept formation, planning, and problem-solving capacities. Evaluation of verbal and visual memory must focus on encoding, recall, storage, learning, and recognition capacities, while assessment of visuospatial functions must focus on visuospatial organization and visuoconstruction capacities.

Alcohol Consumption and Implicit Cognitive Processes

The study of the implicit mechanisms involved in addictive behavior has been considerably developed over recent years. The addictive problem of alcohol-dependence results from a conflict between an urge to drink and the desire to limit alcohol intake. Dual-process models can explain this conflict by the fact that drinking behavior involves two cognitive systems: an impulsive system and a reflexive system.[47] The impulsive system is a "bottom-up" system, based on implicit cognitive processes that play a role in automatic behavior via strong associative memory between alcohol-related cues, outcome, and behaviors. This system therefore reinforces the incentive effects between stimuli related to the addiction (odors, places of consumption, or advertisements related to alcohol, for example) and the addictive behavior. It mobilizes the dopaminergic system of the amygdala–striatal circuit. The reflective system is a "top-down" system based on controlled cognitive processes, in which executive functions regulate the impulsive system to ensure adapted behavior. The underlying network involves various regions of the frontal lobe (lateral inferior prefrontal, dorsolateral, ventromedial, orbitofrontal, and frontoparietal) and the striatum. Finally, the insula plays a decisive role in the articulation of these two systems by translating unconscious interoceptive signals (or somatic states) into conscious subjective experiences (desires or needs) involved in the decision-making process. This system would therefore play a conflict management role between a stimulus related to addiction and a potentially associated somatic state (for example, withdrawal symptoms) in order to guide decision-making.

The interaction between the two systems has been clearly documented in the field of alcohol-dependence.[48] According to this theory, drinking behavior is activated by automatic processes (impulsive system) unless the subject is able to ensure control by mobilizing executive functions (reflective system). The impairment of executive functions observed in alcohol-dependent patients would therefore predispose to drinking behavior dictated by the impulsive system. More precisely, disorders of inhibition capacities and working memory play a predominant role in this dysregulation of the impulsive system by the reflective system,[28, 47, 49-54] thereby resulting in a vicious circle, as chronic excessive alcohol consumption induces working memory and inhibition disorders that are then responsible for dysfunction of the reflective system. Finally, alcohol consumption results exclusively from mobilization of the impulsive system that perpetuates the addictive behavior resulting in continuing deterioration of executive functions.[53]

Cognitive and Brain Recovery

The study of alcohol-dependent patients also constitutes a model of brain plasticity, as an increase of brain volume characterized by increased white matter and gray matter volumes and a reduction of the size of sulci and ventricles is observed right from the first months of abstinence.[55-60] The cognitive effects of this recovery consist of improvement of executive functions and verbal episodic memory.[21, 58, 60-65]

In parallel, it has been shown that new brain regions can be recruited by recently weaned alcohol-dependent patients to compensate for alcohol-related brain damage.[66, 67] Neuroadaptation mechanisms therefore enable patients to maintain a similar level of performance on cognitive tasks to that of control subjects. For example, alcohol-dependent patients recruit neuronal networks parallel to the frontocerebellar circuit normally used by control subjects to perform executive tasks.[68]

However, although abstinence allows an improvement of cognitive functions, this is only achieved after a period of several months. A recent meta-analysis showed that, despite studies showing early cognitive recovery, a global deficit was still present several months after installation of abstinence and the cognitive profile tended to become normal only after 1 year of abstinence, while certain residual cognitive impairments may persist. For example, the presence of visuospatial function deficits may be observed after several years of abstinence, related to the decreased volume of the right parietal cortex.[35]

Cognitive Impairments and Management of Alcohol Abuse

Appropriate management of alcohol withdrawal is mandatory to prevent severe complications like delirium tremens or epileptic seizure. Prevention of Wernicke's encephalopathy relies on thiamine prescription. If benzodiazepines usage and appropriate rehydration are codified, the dose and duration of thiamine treatment remains unclear.[69] **Nevertheless long-term abstinence is the main goal and *cognitive-behavioral therapy* (CBT) and psychosocial programs are necessary. Adjuvant treatments may include: glutamate antagonist (acamprosate) or opioid antagonist (naltrexone).**

The presence of cognitive impairments therefore requires adaptation of the management of alcohol-dependent patients. CBT has been demonstrated to be effective in the management of alcohol-dependence,[70] but it is somewhat paradoxical to propose management that directly involves cerebral structures and cognitive functions altered by chronic alcohol consumption. This management approach may therefore be inappropriate or at least insufficient for a certain number of patients.

The efficacy of CBT would therefore depend on the integrity of certain brain regions of interest. For example, it has been shown in schizophrenic patients that the volume of gray matter in the frontal, temporal (including hippocampus), parietal, and cerebellar regions, brain regions that are also damaged in alcohol-dependent patients, is predictive of the efficacy of management.[71] Similarly, the integrity of the frontocerebellar network, a site of predilection for brain damage in alcohol-dependent patients, would play an essential role in the efficacy of CBT due to its role in executive functioning.[72]

Cognitive behavioral therapy in addiction medicine also requires elaborate cognitive capacities such as episodic, semantic and procedural memories, and executive functions.[23, 73-77] This type of management could therefore be unsuitable for patients with cognitive impairments.[25, 77-79] Various studies have shown that alcohol-dependent patients with the most severe cognitive impairment also have the least favorable prognosis.[80-82]

Cognitive impairment can also influence the expression of individual and environmental factors involved in management, such as self-efficacy, readiness to change, active participation in group therapy, or treatment compliance, as the initial cognitive impairment is predictive of poorer treatment compliance and a decreased self-efficacy. Patients with severe cognitive impairments are also less able to use their own resources during management, in which case the prognosis depends more on the role of external factors such as group therapy or the family support network.[83]

Finally, Le Berre et al.[80] demonstrated the role of cognitive functions in the motivation process of patients to change their addictive behavior. In their study, the authors used the motivational model described by Prochaska and DiClemente,[84] which defines three stages of change as the key to the patient's commitment to the management process: the precontemplation stage (the subject has no intention to change his/her behavior), the contemplation stage (the subject considers changing his/her behavior but remains ambivalent), and the action stage (cessation of consumption and setting-up of strategies to change behavior). Based on this model, the authors showed that episodic memory plays a role in the subject's awareness of the addictive behavior and the need for follow-up. The integrity of this function actually determines the subject's passage from the precontemplation stage to the contemplation stage. Similarly, the integrity of executive functions enables patients to weigh up their decisions to reach the action stage, which can only be implemented when decision-making capacities are preserved. **Cognitive impairment therefore influences the degree of motivation of alcohol-dependent patients, an essential prerequisite to the success of management.**

The presence of cognitive impairments on admission and during the first months of abstinence therefore influences management at various levels by determining the efficacy of treatment and the prognosis for

lasting abstinence. Addiction medicine management must therefore be adapted to alcohol-dependent patients with cognitive impairments.

Cognitive Remediation Therapy

In the light of these findings, it appears essential to propose management based on programs ranging from cognitive remediation to optimal use of the remaining capacities. However, very few addiction medicine units propose cognitive remediation therapy and very few studies have investigated this problem in alcohol-dependent patients. The majority of studies in the field are now relatively old[77, 79] and no longer correspond to current methodological requirements. However, the results of studies conducted in this field are encouraging. A recent study demonstrated that a cognitive remediation program was able to improve divided attention, alert capacities, working memory, and episodic memory. **In addition to cognitive improvement, cognitive remediation therapy also improves other non-cognitive domains, especially psychological aspects (well-being, self-esteem) and craving.[85]**

Studies of the implicit mechanisms involved in addictive behavior also constitute a field of predilection for cognitive remediation. A series of such studies has shown that training working memory and inhibition can lessen the impact of these implicit processes on drinking behavior.[49, 51, 52, 86, 87] However, the methodology of these studies has been the subject of criticism[87] and the observed modification of drinking behavior also does not appear to be related to improvement of inhibition capacities but rather to the formation of new implicit associations promoting an impulsive drinking avoidance response.[50] Finally, only one of these studies has proposed a cognitive remediation therapy that can be transposed to clinical practice[52] and that complies with the clinical criteria defined in the field of cognitive remediation.[88] The results of these studies therefore need to be confirmed by further study protocols satisfying the methodological requirements in the field of cognitive remediation therapy in neuropsychologia.

Conclusion

Data published in the literature suggest that it is essential to take into account the cognitive dimension of alcohol-dependent patients in order to adapt their treatment and to palliate their difficulties in activities of daily living. The brain changes and the profile of cognitive impairments presented by patients with chronic excessive alcohol consumption have now been very extensively documented in the literature. The role of these changes on drinking behavior, especially via the cognitive processes involved in the mechanisms of addiction, also constitutes a rapidly growing new field of research. Finally, the impact of these impairments on the modalities and efficacy of the proposed management is a clinical problem systematically raised in research. The last domain to be developed in the field of management of alcohol-dependent patients is therefore that of cognitive remediation, which can establish the link between the various problems related to cognitive deficits in the clinical management of these patients in order to propose specific targeted follow-up in a remediation therapy program devoted to these impairments.

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

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Multiple-Choice Questions

69. According to the lesson, alcohol consumption stimulates release of:

A. serotonin.

B. dopamine.

C. GABA.

D. None of the above.

70. Patients with alcohol-related cognitive impairments are primarily affected with dysexecutive syndrome which is characterized by impairment in:

A. working memory.

B. mental flexibility.

C. decision-making.

D. All of the above.

71. The areas of the brain that are most susceptible to damage due to chronic excessive alcohol consumption include all of the following except the:

A. neocortex.

B. limbic system.

C. brain stem.

D. cerebellum.

72. Regarding management of alcohol abuse, which one of the following statements is corrct?

A. The goal of cognitive-behavioral therapy (CBT) is short-term cessation of alcohol consumption.

B. CBT is the most suitable treatment in alcohol-dependent patients with cognitive impairments.

C. Cognitive remediation therapy targets and improves cognitive functions and non-cognitive domains.

D. All of the above.

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Best Practices in CME

Cognitive Impairments in Alcohol-Dependent Subjects

By Florent Bernardin, Anne Maheut-Bosser, and François Paille

ID#: L003361

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium of knowledge and daily practice.

CME Lesson Overview

Chronic excessive alcohol consumption induces cognitive impairments mainly affecting executive functions, episodic memory, and visuospatial capacities related to multiple brain lesions. These cognitive impairments not only determine everyday management of these patients, but also impact on the efficacy of management and may compromise the abstinence prognosis. This lesson discusses the need to manage cognitive impairments in this population which may thus lead to enhanced outcomes in alcohol-dependent patients.

Key Point 1: Neurobiology of Alcohol-Dependence

Alcohol-dependence is a chronic disorder, which implies the dopaminergic system. Alcohol consumption acutely stimulates *dopamine* (DA) release from the major terminal area of the mesolimbic DA system, *nucleus accumbens* (NAC).

Key Point 2: Cognitive Impairments

Neuroanatomical alterations can account for cognitive impairments affecting various functions, primarily executive functions such as: working memory, mental flexibility, divided attention, decision-making, and problem-solving.

Key Point 3: Assessment of Cognitive Impairments

The *Montreal Cognitive Assessment* (MoCA) Test appears to be the most appropriate screening test for detection of cognitive impairments in alcohol-dependent patients.

Key Point 4: Management of Alcohol-Dependent Patients with Cognitive Impairments

Cognitive-behavioral therapy in addiction medicine requires elaborate cognitive capacities such as episodic, semantic and procedural memories, and executive functions, and therefore, may be unsuitable for patients with cognitive impairments. Instead, cognitive remediation therapy has been shown to improve cognitive skills, and other non-cognitive domains, especially psychological aspects (well-being, self-esteem) and craving.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Narcolepsy as an Immune-Mediated Disease

Alberto K. De la Herrán-Arita, MD, PhD; and Fabio García-García, PhD

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

KEY WORDS: Narcolepsy • Sleep paralysis • Autoimmune disease

LEARNING OBJECTIVES: Upon completion of this lesson, clinicians will be able to (1) identify the symptoms of narcolepsy in patients; (2) discuss the theorized autoimmune basis for the disease; (3) explain the concept of molecular mimicry and how it may come into play for narcoleptic patients; and (4) discuss the suspected link between vaccination with Pandemrix to prevent against H1N1 and an increase in childhood narcolepsy cases as seen in China.

LESSON ABSTRACT: Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness, cataplexy, hypnagonic hallucinations, sleep paralysis, and disturbed nocturnal sleep patterns. This disease is secondary to the specific loss of hypothalamic hypocretin (orexin)-producing neurons in the lateral hypothalamus. An autoimmune basis for the disease has long been suspected based on its strong association with the genetic marker DQB1*06:02, and current studies greatly support this hypothesis. Narcolepsy with hypocretin deficiency is associated with *human leukocyte antigen* (HLA) and *T cell receptor* (TCR) polymorphisms, suggesting that an autoimmune process targets a peptide unique to hypocretin-producing neurons via specific HLA-peptide-TCR interactions. This concept has gained a lot of notoriety after the increase of childhood narcolepsy in 2010 following the 2009 *H1N1 pandemic* (pH1N1) in China and vaccination with Pandemrix, an adjuvanted H1N1 vaccine that was used in Scandinavia. The surge of narcolepsy cases subsequent to influenza A H1N1 infection and H1N1 vaccination suggests that processes such as molecular mimicry or bystander activation might be crucial for disease development.

COMPETENCY AREAS: This lesson will enhance the clinical knowledge of narcolepsy in clinicians. It focuses on the biological mechanisms and immune related events that may trigger the disease. It aims to increase the reader's knowledge of research on global populations and their findings regarding the development of this disease and its link to a particular type of vaccination.

Introduction

Narcolepsy with hypocretin deficiency is a common sleep disorder that affects approximately 0.02% of the population worldwide and causes disability in 24% of the affected subjects. It is clinically characterized by excessive daytime sleepiness and abnormal sleep-wake patterns. These patients also suffer from cataplexy, a sudden loss of muscle tone triggered by strong emotions such as laughter, and are considered to be fragments of *Rapid Eye Movement* (REM) sleep that intrude into wakefulness, such as hypnagogic (dream-like) hallucinations as they drift off to sleep. All narcoleptic subjects present chronic sleepiness, but the intensity varies across the day and between individuals. This sleepiness is most troublesome during periods of inactivity, though it is often improved temporarily by a brief nap. As a consequence of sleepiness, patients may report inattention, poor memory, blurry vision, diplopia, and automatic behaviors such as driving without awareness.[1–3]

The Hypocretin System

The disorder is caused by the specific loss of hypothalamic neurons producing two hypocretin peptides with high homology with each other, namely, hypocretin-1 and hypocretin-2 (also called orexin A and B), which are comprised of 33 and 28 amino acids, respectively.[4–6] These are produced by proteolytic cleavage of a single precursor protein known as preprohypocretin. There are two cloned hypocretin receptors, HCRT1R and HCRT2R, both of which are serpentine G-protein-coupled receptors.[5] Hypocretin-secreting neurons project from the LH throughout the *central nervous system* (CNS) to neurons involved in the regulation of feeding, sleep-wakefulness, neuroendocrine homeostasis, and autonomic regulation.[7] Hypocretin knockout mice and dogs with null mutations in the HCRT2R gene develop narcolepsy, indicating that the loss of this peptide is causal for development of the disease.[8–10]

Moreover, narcoleptic patients typically have low hypocretin *cerebrospinal fluid* (CSF) levels, which can be explained by the loss of over 90% of their hypocretin-producing neurons.[11–14] This loss of hypocretin-producing cells is selective rather than general or regional destruction, as *intermingling-melanin concentrating hormone* (MCH)-producing neurons appear to be unaffected in the same narcoleptic patients.[13, 14] This specific depletion of hypocretin-secreting neurons led to the hypothesis that narcolepsy is an autoimmune driven process within the hypothalamus.

The Immune System and Narcolepsy

An autoimmune basis for the hypocretin cell loss in narcolepsy has long been suspected based on its strong genetic association with selected HLA alleles.[15] These alleles encode multiple subtypes of *Major Histocompatibility Complex* (MHC) classes I and II proteins, which present foreign peptides to T cells during infections, triggering immune responses via TCR activation. In the case of autoimmunity, self-peptides are hypothesized to be mistakenly recognized as foreign, leading to tissue destruction, often occurring in context of specific HLA alleles.

Among autoimmune diseases, narcolepsy may be uniquely positioned to demonstrate autoimmunity in humans. First, narcolepsy occurs nearly exclusively with DQ0602, a heterodimeric a/b class II protein encoded by HLA DQB1*06:02 and DQA1*01:02, two gene variants found together on the same haplotype.[15] Second, a specific amino acid variant in the *T cell receptor alpha* (TCRa) locus J24 segment encodes the chain of the heterodimeric a/b TCR molecule also confer increased risk,[16] indicating a crucial role for TCR containing this segment in the immunological synapse in narcolepsy. Finally, studies have shown increased rates of narcolepsy onset in children following exposure to streptococcus pyogenes,[17] selected H1N1 vaccine preparations,[18–20] and influenza A H1N1 infections.[21] These findings strongly suggest that some T cells that can be activated by H1N1 epitopes also lead to hypocretin neuron destruction. A parsimonious explanation would involve mimicry between H1N1 and hypocretin peptide sequences, as hypocretin is the only known protein specific for these cells.

Clinically, the association between infections and autoimmune disorders is a well-known phenomenon. Viral, bacterial, and parasitic pathogens may cause

autoimmune inflammation of a variety of organs, including the heart and bowel, as well as the peripheral nervous system and the CNS.

Autoimmunity and Narcolepsy

Characterization of the cellular and molecular basis of hypocretin cell death in narcolepsy is extremely important both to understanding the pathogenesis and to achieving the ultimate goal of designing specific treatments. Although immune responses are complex, involving both humoral and cellular immune components, some autoimmune diseases are predominately $CD4^+$ T cell mediated, whereas others seem to be primarily antibody mediated.

Viruses and other infectious insults are implicated in the etiology of many human autoimmune diseases. **In the case of narcolepsy, streptococcus pyogenes and influenza A H1N1 infection and H1N1 vaccination have been strongly correlated to the onset of the disease.**[17–21] There are various mechanisms by which infection can lead to the initiation of an autoimmune response; however, intense efforts to identify an underlying pathogen have failed in the vast majority of autoimmune disorders. Two major hypotheses have been raised to explain how infections may induce autoimmunity in the CNS and more specifically hypocretin-neuron destruction in narcolepsy: bystander activation and molecular mimicry. Although infectious diseases may trigger cerebral autoimmune diseases by other mechanisms, such as activation of CNS *antigen-presenting cells* (APCs) or inhibition of immunosuppressive cytokines, bystander activation and molecular mimicry are currently the most intriguing and most likely mechanisms.

Bystander Activation of Autoreactive T Cells

It is well known that cytotoxic T cells are polyclonally stimulated during viral infections. Cytokines secreted by antigen-responsive cells at infectious foci may directly stimulate surrounding T cells by cytokines in the absence of direct triggering of the T cell receptor.[22] Thus, a proinflammatory microenvironment creates a fertile field, allowing activation of, but not pathogen-specific T cells, which subsequently may damage hypocretin cells.[23] This latter scenario may become particularly relevant when underlying infection causes tissue destruction, thereby deliberating host cell proteins, which can be presented by APCs to autoreactive bystander T cells.

In addition, epitope spreading may induce autoreactive hypocretin T cells. During infection, pathogen-specific T cells develop in a hierarchical manner, being directed against immunodominant epitopes first. Subsequently, the T cell response may be generated against further, less dominant epitopes of the same protein or against epitopes of a different protein such as a hypocretin cell autoantigen. Such epitope spreading is useful for the host to optimize a T cell response during an ongoing infection but bears the unwanted risk of stimulation of potentially harmful autoreactive T cells.[24] Epitope spreading, combined with an increased amount of host hypocretin cell epitopes generated by APCs from destroyed host cell tissue and the adjuvant effect on an infection, may create a fertile field for the development of cerebral autoimmune reactions.[25]

In addition to this mode of bystander activation of autoreactive T cells, virus-specific T cells also might initiate bystander activation against hypocretin neurons. For example, virus-specific T cells migrate to areas of virus infection/antigen where they encounter virus-infected cells that present viral peptides in the context of MHC class I molecules to virus-specific T cells.[26, 27] The $CD8^+$ T cells recognize these infected cells and release cytotoxic granules resulting in the killing or death of the infected cells. Under these circumstances the dying cells, the $CD8^+$ T cells, and inflammatory cells (macrophages) within the inflammatory focus release cytokines such as *tumor necrosis factor* (TNF), TNF-β, *lymphotoxin* (LT), and *nitric oxide* (NO), which can lead to bystander killing of the uninfected neighboring cells. This results in additional immunopathology at sites of infection. This also appears to be true for $CD4^+$ T cells that can recognize peptide in the context of class II molecules. Cytokines released by the $CD4^+$ T cells can directly kill uninfected cells, but also macrophages can kill uninfected cells in a bystander manner.[28, 29] However, this latter scenario seems rather improbable, as MCH neurons are intermingled with hypocretin neurons and MCH-producing cells are intact in narcoleptic patients.[13, 14]

Molecular Mimicry

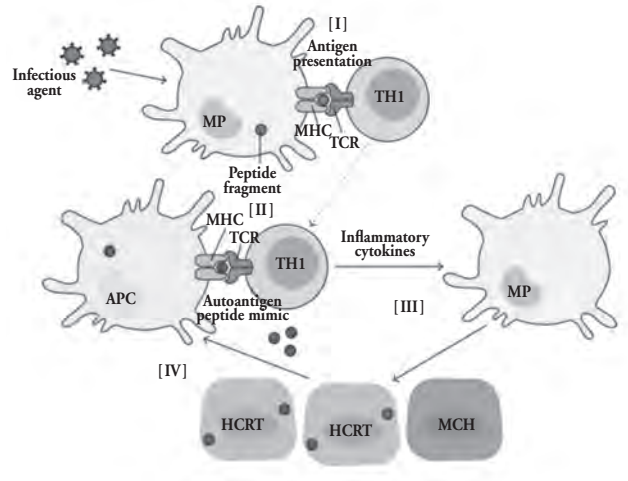
The attractive hypothesis of the concept of molecular mimicry is based on the existence of structural similarities between antigenic determinants of a pathogen and the host[30] (Figure 1(a)[I]). Consequently, a single T cell receptor may bind to structurally related antigens (Figure 1(a)[I]), which may differ in their amino acid sequence (Figure 1(b)[I] and 1(b)[II]), bound to one or several MHC molecules. This TCR degeneracy implies that T cell responses to pathogen-specific antigens may result in the activation and expansion of T cells (T helper 1, TH1) cross-reactive with self-antigens. TCR recognition is remarkably flexible: a single TCR is able to respond to different peptides (Figure 1(b)[I] and 1(b)[II]) and can react with different peptide-MHC complexes of similar charge distribution and overall shape. Disease-inducing epitopes are those peptides of autoantigens that can be presented by MHC class II molecules on APCs to autoreactive $CD4^+$ T cells (Figure 1(a)[II]).[24, 25, 30]

In the case of narcolepsy, molecular mimicry would involve processing and presenting bacterial and/or viral peptides in the context of MHC DQB1*06:02 (Figure 1(a)[I]), which would activate a population of cross-reactive T cells present in predisposed individuals (Figure 1(a)[II]).

This could easily explain the data obtained following the 2009–2010 H1N1 influenza pandemics, where European investigators reported a significant 6–9-fold increase in the risk of developing narcolepsy after pandemic H1N1 (pH1N1) flu vaccination in Scandinavian children.[18–21, 31–37] It is suspected that vaccination with Pandemrix, a pH1N1 vaccination formulation containing the adjuvant AS03, a combination of squalene and alpha-tocopherol,[18, 19] perhaps together with other environmental factors, contributed to the increased incidence of narcolepsy in HLA DQB1*06:02-positive children. In most, if not all the models where molecular mimicry has been used to induce an autoimmune disease, an adjuvant or an actual infection is required. The

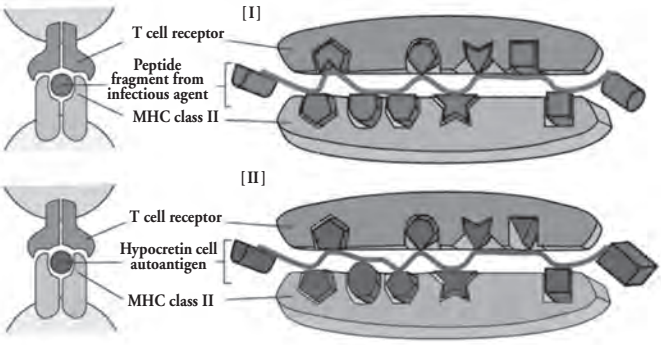
Figure 1:

(a) Molecular mimicry describes the activation of cross-reactive TH1 cells that recognize both the microbial epitope [I] and the autoantigen [II]. Activation of the cross-reactive T cells results in the release of cytokines and chemokines [III] that recruit and activate monocytes and macrophages, which mediate self-tissue damage. The subsequent release of self-tissue antigens and their uptake by APCs perpetuates the autoimmune disease [IV].



(a)

(b) Molecular mimicry at the MHC/TCR synapses level. Molecular mimicry between infectious agents (H1N1 and/or streptococcus pyogenes) and hypocretin neuron autoantigens. Sequence and structural homology between foreign [I] and self-peptides [II] are required for molecular mimicry to occur. The MHC binding groove selects the peptide fragment with a specific amino acid sequence in the context of DQA1*01:02-DQB1*06:02. The TCR recognizes a presented peptide with a specific amino acid sequence [I and II]. Activated CD4+ T cells cross-react and recognize hypocretin neuron autoantigens as foreign molecules, prompting an autoimmune response against hypocretin neurons [II].



(b)

fact that the AS03-containing vaccine was particularly associated with increased onset could be the result of the strength and nature of the AS03 adjuvant that would catalyze molecular mimicry between H1N1 proteins and hypocretin cell containing proteins. This suggests that, in addition to having a cross-reacting disease, inducing epitope sufficient activation of APCs is required.

Moreover, the correlation between influenza A infection and the onset of narcolepsy was further strengthened by reports from China showing that onset in children spiked following the H1N1 influenza pandemic of 2009.[21] Interestingly, the majority (>95%) of these patients had not received H1N1 vaccination, indicating that naturally occurring influenza A infections may increase the susceptibility of developing this disorder.

These findings strongly suggest that some T cells that can be activated by H1N1 epitopes could lead to the destruction of hypocretin-producing neurons.

Conclusion

The autoimmune basis for narcolepsy is supported by several recent studies from all over Europe, which reported significant increase in the incidence of narcolepsy with cataplexy in children vaccinated with Pandemrix as compared to those in the same age group who were not vaccinated,[18–21, 31–37] suggesting that in genetically susceptible children, Pandemrix vaccination may alone be sufficient to initiate or precipitate narcolepsy. However, the precise mechanism of disease pathogenesis and etiology still remains an enigma.

Some researchers have hypothesized that narcolepsy could be a B cell autoimmune-mediated disease and that autoantibody production may trigger hypocretin cell destruction. Unfortunately, these studies found moderate[17, 24] to nonexistent production of antibodies[25] in recent-onset narcolepsy patients.

There is evidence for the concept of molecular mimicry playing an important role in this scenario, while bystander activation of T cells appears to be of minor relevance.

It is very conceivable that virus infections, such as influenza A H1N1 virus, could lead to significant activation of APCs such as dendritic cells. These activated APCs could potentially activate preprimed autoreactive T cells, which can then initiate an autoimmune process against hypocretin cells. In addition, virus-specific T cells could migrate to the CNS, where they encounter virus-infected cells that present viral peptides in the context of MHC class I molecules to virus-specific T cells. The $CD8^+$ T cells could recognize these infected cells and release cytotoxic granules resulting in the destruction of hypocretin neurons.

Unfortunately, evidence of the involvement of $CD8^+$ T cells and MHC class I in the pathology of narcolepsy is virtually nonexistent.

It is rather simple to visualize how molecular mimicry could induce autoimmunity, given that it involves a shared immunologic epitope between a microbe and the host. Disease-inducing epitopes are those peptides of autoantigens that can be presented by MHC class II molecules on APCs to autoreactive $CD4^+$ T cells.

The influenza A virus has shown to be one of the most likely environmental factors capable of precipitating autoimmune narcolepsy. Upon influenza A infection, $CD4^+$ T cell activation could be achieved after antigen presentation of MHC class II molecules in the context of DQB1*06:02. It is plausible that these "peptide mimic" specific T cells could cross-react with self-epitopes in hypocretin neurons, thus leading to narcolepsy.

The link between autoimmunity and narcolepsy is clearly a consequence of genetic factors coupled with exposure to environmental factors. The total infectious history of each individual and exposure to other environmental agents has to be considered and tracked. Some of the factors might be disease promoting, whereas others might be protective. In the future it will be important to monitor such environmental factors individually to assess their relative contributions to narcolepsy. The identification of both the underlying autoantigen(s) as well as the causative pathogen is a pending challenge.

Appendix:
Abbreviations

APC:	Antigen-presenting cell
HCRT:	Hypocretin
MCH:	Melanin-concentrating hormone
MHC:	Mayor histocompatibility complex
MP:	Macrophage
TCR:	T cell receptor.http://www.ncbi.nlm.nih.gov/myncbi/collections/

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

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Acknowledgment: A Grant 133178 to FGG from CONACYT supported this work.

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Multiple-Choice Questions

73. All of the following are symptoms of narcolepsy, *except*:

A. chronic, daytime sleepiness.

B. hallucinations when falling asleep.

C. severe, sudden-onset snoring.

D. sudden loss of muscle tone following an emotional experience.

74. According to the lesson, patients with narcolepsy are likely to report which of the following:

A. enhanced visual abilities.

B. increased attention span.

C. stomach upset.

D. automatic behaviors, like driving without awareness.

75. All of the following factors are strongly correlated to the onset of narcolepsy, *except*:

A. streptococcus pyogenes.

B. influenza H1N1.

C. vaccination against influenza H1N1.

D. a tetanus vaccination.

76. According to the lesson, molecular mimicry occurs when:

A. there are structural similarities between antigenic determinants of a pathogen and the host.

B. a virus disguises itself as a common protein found in the host organism in order to survive.

C. an individual has a weakened immune system.

D. an individual has failed to be vaccinated against H1N1.

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Best Practices in CME

Narcolepsy as an Immune-Mediated Disease

By Alberto K. De la Herrán-Arita, MD, PhD; and Fabio García-García, PhD

ID#: L003362

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium of knowledge and daily practice.

CME Lesson Overview

Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness, cataplexy, hypnagonic hallucinations, sleep paralysis, and disturbed nocturnal sleep patterns. This disorder may be linked to autoimmune activity resulting from infection with the H1N1 influenza virus, vaccination against the H1N1 virus, and certain other pathogens. Understanding how molecular mimicry or bystander activation may play a role in the development of this condition could play a vital role in understanding different options for treatment and management of this condition.

Key Point 1: Symptoms of Narcolepsy

The symptoms of narcolepsy include excessive daytime sleepiness, abnormal sleep-wake patterns, cataplexy, and hallucinations when falling asleep.

Key Point 2: The Hypocretin System

Narcoleptic patients typically have low hypocretin cerebrospinal fluid levels, which can be explained by the loss of over 90% of their hypocretin-producing neurons.

Key Point 3: The Immune System and Narcolepsy

An autoimmune basis for the hypocretin cell loss in narcolepsy has long been suspected based on its strong genetic association with selected HLA alleles.

Key Point 4: Autoimmunity and Narcolepsy

In the case of narcolepsy, streptococcus pyogenes and influenza A H1N1 infection and H1N1 vaccination have been strongly correlated to the onset of the disease.

Key Point 5: Molecular Mimicry and Narcolepsy

In the case of narcolepsy, molecular mimicry would involve processing and presenting bacterial and/or viral peptides, which would activate a population of cross-reactive T cells present in predisposed individuals.

The information presented herein is based upon the content in the associated CME lesson. If you have comments or feedback about this page, please send your feedback via email to: **editorial@hatherleighpress.com** and reference the ID number under the title to which you are referring. We will review your commentary, which may be used for publication.

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Notes

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Pediatric Pain Assessment and Management: A Systematic Approach Including Psychiatric Assessment

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No commercial support was used to develop this CME lesson.

KEY WORDS: Pain Management • Pediatrics • Palliative Care

LEARNING OBJECTIVES: This lesson will provide an overview of pain management for children. It aims to help clinicians: (1) understand an evidence-based, systematic approach to pediatric pain management in acute-, chronic-, and palliative-care settings; (2) review widely accepted and potentially adjunctive treatment options while assessing the possible comorbidity of psychiatric illnesses; (3) understand common barriers to effective treatment; and (4) assist clinicians in reflecting on their own knowledge, skills, and attitudes about pain management.

LESSON ABSTRACT: Pain assessment and management are common needs in pediatric healthcare that, despite many efforts, remain largely unmet. A child might present with acute pain for an intermittent issue or might have acute or chronic pain in the context of a chronic or life-limiting illness. Such situations might be further complicated if the child also has a co-occurring psychiatric illness. The aim of this lesson is to improve clinicians' understanding of how to evaluate pain type(s) and treatment(s) (e.g., medications and therapies), using a systematic approach. This lesson will systematically review the best practices for evaluating and managing pediatric pain. Pain management in children is multimodal and must consist of evaluations using standardized tools and systematic medication increases. Pain often increases psychological distress and the risk of comorbid psychiatric illnesses such that patients must also be regularly evaluated for such ailments, as they might benefit from therapy and medication treatments. Moreover, children with chronic and life-limiting illnesses require additional care coordination to help co-manage their pain and can benefit from wrap-around services, such as cognitive-behavioral therapy or palliative care, on a case-by-case basis. Pain-management best practices require patient- and systems-level approaches in evaluating and treating pain. For children with life-limiting illnesses, guidelines recommend palliative care that includes comprehensive services for pain control in conjunction with curative therapies. Albeit many barriers presently block child patients' access to palliative care, key components of pain management in children are multimodal and achievable, regardless of the cause of a child's pain.

COMPETENCY AREAS: This lesson addresses the gap in medical knowledge, patient care, and employment of evidence-based medicine concerning pain management for children. It is the hope of the present lesson's authors that implementing pain-management best practices in this area will improve patient-centered care for children in pain.

Introduction

Pain is a complicated and, often, undermanaged condition, especially for children. It is now recognized as multidimensional and can best be understood within the context of a biopsychosocial model that incorporates biological, environmental, and cognitive behavioral mechanisms in the development and maintenance of treatment.[1] Emotions, behavioral responses, beliefs, attitudes, and spiritual and cultural ideas about pain and pain control all alter the way pain is experienced by modifying the transmission of noxious stimuli to the brain.[2] Children can be especially sensitive to the emotional aspects of pain because their understanding of painful experiences is still developing.[3]

Despite myriad efforts to educate clinicians on the idea that pain is a common symptom in pediatric healthcare, there is still a largely unmet need for pain management in this realm. Approximately 15% of children live with chronic pain,[4] and a vast majority (78%) of pediatric *emergency-department* (ED) visits involve some form of intense pain.[5] Studies repeatedly show that pain, especially chronic pain, is underdiagnosed and, consequently, under-treated.[6-15] Crucially, many children live with multiple kinds of pain, requiring the use of diverse measurement and treatment modalities.

Factors that contribute to the under-treatment of pediatric pain include the knowledge, attitudes, and behaviors of providers and patients' family members. Pain is difficult to manage, for both providers and parents. Additionally, pain can have many components, yielding various pharmacological options for controlling pain. In this lesson, we will discuss pain management best practices, as well as some of the barriers to the successful treatment of acute, chronic, and palliative pain and to pain exacerbated by psychiatric illnesses in children.[14]

Case Study:

Initial Presentation

A 13-year-old African-American girl with a history of sickle-cell disease, SS type, presented to the hematology clinic with her mother for a follow-up after an ED visit for an acute pain crisis.

History

The patient, well-known to the hematology clinic, had presented to the ED the day before, complaining of severe pain in her left leg and thigh, the most common pain sites for her. This had been the patient's seventh ED visit in as many months. In the ED, the patient was afebrile, had a normal physical exam except for an antalgic gait, and had no noted swelling or warmth in the thigh, knee, or leg. The patient's x-rays were normal. She was given IV hydration and doses of IV ketorolac and oral morphine, the latter of which was higher than her usual dosage, and this resulted in an apparent lessening of her pain. She was sent home after 6 hours with a prescription for a 3 days' supply of this higher dosage of oral morphine and instructed to follow up with the hematology clinic the next day.

The following day the patient reported continued, but less severe, leg and thigh pain. Medications she took at home included folic acid, hydroxyurea, and the oral morphine prescription she was to fill in the event of a pain crisis. The patient's mother said she had not filled the hydroxyurea prescription because it did not seem to make a difference in the patient's pain during pain crises. She said she had not filled the morphine prescription either because she did not want her child to become dependent on such drugs. The patient was taking folic acid daily and had been taking *acetaminophen* (Tylenol) every 4 hours since her ED visit.

Additionally, the patient had repeatedly told her mother over the preceding 2 months that she felt more fatigued and wasn't "enjoying things" as she normally did. She had stated, moreover, that she was not sleeping well. Her mother found the patient's journal, in which the patient had written that she did not want to "go on like this."

Pain Definitions

Before discussing the above-outlined case, this lesson will provide some background on pain assessment and management. *Acute pain* is one of the most common adverse

experiences among children and can result from illness, injury, and necessary medical interventions like surgery.[3] Acute pain is often viewed as having a "sudden onset, is felt immediately following an injury, and is severe in intensity but usually short-lived. It arises as a result of tissue injury, stimulating nociceptors, and generally disappears when the injury heals."[2] Yet, despite their knowing that children experience pain and despite the availability of analgesic at-home medication, clinicians often inadequately treat acute pain in children.[7, 9]

Meanwhile, *chronic pain* in children is, perhaps, more widespread. Some epidemiological studies indicate that approximately 30% of children and adolescents experience pain lasting 3 months or longer.[16] It is often associated with functional disabilities that limit children's abilities to develop and learn properly. Chronic pain can begin as acute pain but eventually persists for long periods or recurs due to the persistence of noxious stimuli or the repeated exacerbation of an injury.[2] It can "negatively affect all aspects of daily life, including physical activities, school attendance, sleep patterns, family interactions, and social relationships, and it can lead to distress, anxiety, depression, insomnia, fatigue, [and] mood changes, such as irritability and negative coping behavior."[2] The most common pediatric chronic-pain complaints include migraines, recurring abdominal pain, and general musculoskeletal pain.[16]

Many studies have shown that children and adolescents, especially girls, with persistent pain express higher levels of anxiety and depression.[16, 17] The expression of depressive symptoms as a result of pediatric pain has been linked to greater school impairment, as well as with perceptions of greater pain intensity.[16] These experiences exist independently and require separate assessments.

Evaluating and Measuring Pain

The patient presented in the above scenario reports experiencing multiple kinds of pain simultaneously: her acute and chronic physical pains are exacerbated by a likely psychiatric illness. Measuring pain can be difficult, and it requires breaking pain down into its components.

One of the first steps in treating pain effectively is to assess a pain's severity. There are numerous methods available for assessing pain in children, from direct questioning to formal, validated written scales. Many age-appropriate pain-rating scales have been developed over the past 3 decades.[3] Frequently used scales include the *Faces Pain Scale-Revised*, the *Pieces of Hurt/Poker Chip Tool*, the *Visual Analogue Scale*, and the *Oucher Photographic and Numerical Rating Scale*.[2] The Society of Pediatric Psychology Pain Assessment Task Force's Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials has recommended these scales for measuring pain intensity in children with acute and chronic pain. Measuring a pain's duration can, for instance, help a clinician determine whether the pain is acute or chronic, and children who live with pain often become trained experts in their pain once these tools are used repeatedly, thus allowing them to offer accurate scores quickly when chronic pain flares up acutely.

In addition to measuring the level of acute and chronic pain, children, especially those with chronic pain and those facing end-of-life issues, need to undergo regular assessments for comorbid psychiatric conditions. Depression- and anxiety-screening tools for children and adolescents exist and can be helpful in such assessments. The *Children's Depression Inventory* can be used in children ages 7 and older, and the *Center for Epidemiological Studies' Depression Scale for Children* can be used for children over age 12. Likewise, the *Beck Depression Inventory* can be used in adolescents age 14 and older.

For its part, the *Children's Depression Inventory* requires a first-grade reading level, while the others require a sixth-grade reading level. Meanwhile, the *Pediatric Symptoms Checklist* is another screening tool; while it is not specifically focused on depression, it can help identify patients in need of further assessment, and crucially, it can be completed by a parent or guardian.[18] Primary care providers can then integrate information gleaned from these assessments into their understanding of how to treat the pain, depression, and anxiety that cause their patients' functional disabilities.

Pain Management

Acute and Chronic Pain:

Once a patient's pain has been measured and his/her clinicians and family members have decided if the pain is

acute or chronic and whether a psychiatric illness might be contributing to the patient's presentation, the pain should be managed. Yet, treating pain can be as difficult as assessing it. Geeta et al. describe four key concepts clinicians should bear in mind when using analgesics with children: "by the ladder, by the mouth, by the clock, and by the child."[19] **"By the ladder" refers to the *World Health Organization's* (WHO's) analgesic *ladder*, according to which a clinician should step up to the second rung for moderate to severe pain when acetaminophen and *non-steroidal anti-inflammatory drugs* (NSAIDs) no longer or never did relieve the patient's pain.[20]** This schema offers a choice of analgesic medicines based on the severity of the child's pain. When treated with oral pain medications, children are more easily treated at home, obviating the additional pain of receiving injections.

"By the clock" is a reminder to give medications at regular intervals, rather than waiting for the patient's pain to become severe. "By the child" refers to prescribing medication appropriate for the individual child and the symptoms she is experiencing.[19]

According to WHO's analgesic ladder, *ibuprofen* (Advil, Motrin) and other NSAIDs are appropriate for children age 6 months and up, and acetaminophen should be considered the first options for children suffering mild pain. In children suffering moderate to severe pain, opioid administration is highly advised.[2] Importantly, opioids can and should be combined with acetaminophen and ibuprofen to ensure that the lowest dose of the opioid possible is used. The WHO analgesic ladder has recently been modified from a three-step to two-step schema. The three-step approach, introduced in 1986, recommended the use of codeine as a weak opioid in treating moderate pain, but this is now considered outdated and dangerous advice (see *A Note on Codeine* below). **The newer two-step approach allows for the use of stronger opioids, like morphine, in smaller dosages for moderate pain. For moderate to severe pain, WHO recommends morphine as the first line of treatment; it also recommends *fentanyl* (Duragesic, Actiq) *hydromorphone* (Exalgo, Dilaudid-hp), *methadone* (Methadose, Diskets), and *oxycodone* (Roxicodone, Oxycontin) as additional options.[2]**

A Note on Codeine

There are well-known safety and efficacy issues related to codeine, vis-à-vis genetic variability in its biotransformation, and it is no longer recommended for children and adolescents.[2, 21] Codeine is a prodrug converted by the CYP2D6 enzyme into its active metabolite, morphine. A large number of children under age 6 have very limited metabolisms, and such children therefore experience no analgesic effects from codeine at all. Moreover, some children metabolize codeine quickly at the plasma level, such that the resulting morphine can become hazardous. Consequently, the U.S. *Food and Drug Administration* (FDA) has issued warnings since 2012 regarding prescribing codeine to children.[2, 21]

Psychiatric Comorbidities that Exacerbate Pain

If and when a child is diagnosed with a psychiatric illness, care coordination is crucial to managing her pain. Increased emotional distress can often increase perceptions of pain. Children and adolescents often benefit from combinations of medication and therapies that address their mental-health needs. Although most do not do so, primary care providers, despite black-box warnings, sometimes feel confident in prescribing first-line anti-depressants.[22] *Fluoxetine* (Prozac) and *escitalopram* (Lexapro) are the only *selective serotonin-reuptake inhibitors* (SSRIs) approved by the FDA for use in treating depression; however, first-line medications *citalopram* (Celexa) and *sertraline* (Zoloft) are also often prescribed. When discussing medication options with family members, it is important to keep in mind that SSRIs must be taken for weeks or months before improvements to a patient's mental state can be observed. Critically, educating family members on the connections between the mind and body—and, consequently, between psychotherapy and pain treatment—can also prove beneficial. Emotional stress and fear can both be risk factors for and result in pain and functional disabilities. Children with chronic pain can experience sleeping difficulties that must also be addressed through comprehensive pain assessments.[2]

Table 1:
List of Self-report Measuring Tools for Pain Intensity

Tool and acronym (original citation)	Applicable age range and method	Comments (strengths, weaknesses and limitations, cultural validation)	Language	Ease of use	Availability, cost, source
Faces Pain Scale-Revised (FPS-R) (*41*)	4–12 years – self-report by child	Faces are line drawings with no ethnicity distinctions ranging from a neutral expression to one of intense pain but without tears. Simple, quick to use and requires minimal instructions.	Available in 47 languages	Easy to administer and score, readily reproducible by photocopying.	All translations available at no cost at: http://www.iasp-pain.org/fpsr/
Pieces of Hurt tool/ Poker Chip tool (*42*)	3–12 years – self-report by child	Based on concrete ordinal rating scale. Require confirmation that size-sorting task is developed in children. Weaknesses include cleaning the chips between patient use, the potential for losing chips and the limited number of response options (0–4). Only modest evidence of reliability and validity in preschool children between 3 and 4 years.	Arabic, English, Spanish, Thai	Simple, quick to use, require minimal instruction, easily reproducible, transported and disinfectable.	Instructions in English available at: http://painresearch.utah.edu/cancerpain/ch14.html

Table 1: (cont.)
List of Self-report Measuring Tools for Pain Intensity

Tool and acronym (original citation)	Applicable age range and method	Comments (strengths, weaknesses and limitations, cultural validation	Language	Ease of use	Availability, cost, source
Visual Analogue Scale (VAS)	Above 8 years--self-report by child	Sensitive to change correlates significantly with parents' and/or caretakers' ratings of children's pain. Retrospective self-report has more recall bias, requires a high degree of abstraction to indicate, on a line, the different verbal expressions for varying pain intensity and unpleasantness.	Chinese, English, French, Italian, the main Nigerian languages (Hausa, Igbo, Yoruba) (44), Portuguese, Spanish	Easy to administer and Score, readily reproducible, but photocopying may alter the scale by increasing or decreasing the length of the line.	Available at no cost at:http://www.partnersagainstpain.com/printouts/A7012AS1.pdf
(a) The Oucher Photographic (b) 0-10 Numerical Rating Scale (45)	(a) 3-12 years (b) Above 8 years-- self-report by child	(a) A colour photographic scale of a child's face with different pain expressions for younger children and a NRS of 0-10 for older children. There are four versions of the photographic scaled: African-American, Asian, Caucasian and Hispanic child populations. (b) The NRS can be administered verbally by asking the child to verbally estimate his//her pain level on a 0-10	English	Simple to use. (a) The Oucher photographic NRS requires costly colour printing. (b) The NRS can be administered verbally without any printed material.	Available at: (a) http://www.oucher.org/differences.html (b) http://painconsortium.nih.gov/pain_scales/NumericRatingScale.pdf

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WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses.

Table 2.1: List of self-report measuring tools for pain intensity
http://www.who.int/medicines/areas/quality_safety/guide_perspainchild/en/

Palliative Care

Extreme cases of pain combined with psychiatric illness emerge when a child has a life-limiting illness. The *Institute of Medicine* (IOM) and the American Academy of Pediatrics recommend children with life-limiting illnesses receive pediatric-specific palliative services. In the US, palliative care programs for children often mirror adult models by providing services only during the final 6 months of life.[23] Given the variable nature of most life-limiting childhood conditions, however, this brief period has been proven inappropriate.[23] The IOM has instead recommended an alternative model in which palliative care is initiated immediately upon diagnosis of a life-limiting illness. Palliative care should therefore not replace but coincide with ongoing curative therapies and pain-management techniques. This model has also been endorsed by WHO.[2]

The optimal model for palliative care treats a wide spectrum of children's needs, both physical and psychiatric, and it also recognizes that children's families should receive palliative care.[24] Parents and siblings might require support, counseling, respite, expressive therapies (e.g., music, play, and art), and bereavement counseling. And yet, such integrative interventions should go beyond a palliative-care team's offering its services to the child and his or her family. Integration also requires that the child's primary-care provider, and possibly his or her specialty providers, know and understand the scope, intensity, and duration of the palliative-care services delivered.[14]

Barriers to Pain Management

Barriers to adequate pain management persist despite the aforementioned, well-articulated, long-standing guidelines. Importantly, providers and parents might be reluctant to administer analgesics to children due to a lack of knowledge, concerns regarding addiction or dependence, or their beliefs that medication should be used only as a last resort. Many people also view antidepressant use as stigmatizing and stunting to children's growth and development.

When barriers exist on the patient level, there are several steps that can be taken to reduce them.[14] Physicians can bridge gaps in parents' understandings of pain and analgesics through education and by providing anticipatory guidance. Physicians should discuss what to expect regarding a patient's pain with the family, ideally prior to a child's suffering pain, as in preoperative stages. Importantly, physicians can prepare children for future pain episodes by prescribing emergency pain medications. Moreover, practitioners should assess parents' understandings of and concerns regarding potential addiction to opiate and non-opiate pain medications.[14] Physicians should administer pain scales and psychiatric assessments at measured intervals to ensure adequate and ongoing pain management for every child. The child's primary-care provider should coordinate all communication between subspecialists and families to ensure all parties are aware of any pain-treatment regimen and its potential side effects.[14]

When barriers persist on the practice or system level, additional thought on how to address them might be required. For example, it is unclear who should primarily manage chronic pain. Ironically, most pediatricians, generalists, and specialists alike do not see themselves as primarily responsible for managing severe, chronic pain.[8, 9, 15, 25] They believe the primary responsibility for this lies with pain specialists. Yet, given the paucity of pain specialists, primary-care providers should offer additional pain-management support. Additionally, both physicians and parents have voiced concerns about opioid side effects, believing that opioids are inappropriate for treatment of non-cancer-related pain and are significantly linked to patient addiction.[14] Continued education on WHO's two-step approach to pain management as described above can be used to effectively argue the need to manage persistent pain in children pharmacologically.

Most disconcerting, though, is the lack of referrals to palliative-care services for children with life-limiting illnesses. Despite well thought-out care models, pediatricians do not readily refer patients to palliative care early on. (For more information, see Children's Hospice International.)[24] This might result from social discomfort in approaching families about this option or from a lack of knowledge. In a national survey of pediatricians,[13] a majority saw *palliative care* as synonymous with *hospice care*, and roughly 25% more reported not knowing that these two types of care were defined differently. (Again, while not the topic of this lesson, more information can be found at Children's Hospice International. In brief, palliative care can and should co-exist with curative and/or hospice management for life-threatening illness

throughout the duration of illness; hospice care is focused on end-of-life care and often comes into play during the last weeks and months of life.)[24] Furthermore, the same survey found that more than one-third of respondents did not have or did not know if palliative-care services were available in their areas, and only half had ever referred patients to palliative-care providers. Pediatricians also reported that they viewed families as reluctant to accept palliative care, as they believed parents saw palliative care as "giving up"; they said this was why they were reluctant to refer patients to palliative-care providers.[25] Policy makers, health organizations, and government agencies should develop palliative programs or expand enrollment in existing programs to address these issues.[13]

More recently, multidisciplinary, pediatric-pain rehabilitation centers have gained increasing support as treatment facilities of choice among chronic-pain sufferers.[16] Relatively few of these treatment centers exist worldwide. However, the combination of exercise and physical and occupational therapies they provide are often essential to patients' full recoveries. *Cognitive-behavioral therapy* (CBT) interventions for coping with pain and anxiety are also integral, reflecting how pain assessments should be incorporated into treatment for psychiatric illnesses and distress.[16] The primary goal of CBT treatment in addressing chronic pediatric pain is to teach children self-regulation techniques. This can include teaching them relaxation techniques, such as progressive muscle relaxation, biofeedback, and guided imagery. It can also include cognitive strategies like cognitive restructuring, problem solving, and the creation of fear hierarchies to help them perceive pain as less debilitating.[16]

The Case Study Reviewed

In light of the earlier information, the girl presented in the above scenario would benefit from a multimodal approach to pain management. First, her care providers should better educate her and her parent regarding pain medications, as compared with preventive and long-term medications. **An opioid medication like morphine is considered an appropriate first-line medication for children with sickle-cell disease in crisis, and increasing the dosage for acute flare-ups is necessary.** Education and counseling should dissuade the parent from fearing addiction. Moreover, it might help if the patient is further evaluated for comorbid psychiatric illnesses, given her expression of increased fatigue and anhedonia. Of significant concern are her journal entries containing possible passive suicidal ideation. A comprehensive safety evaluation—determining (1) whether she has devised a plan to end her life prematurely, (2) whether she has a history of suicide attempts, (3) whether she has a history of self-injury, (4) whether she has a family history of psychiatric illness, and (5) whether any guns are kept in her home—is critical. A more comprehensive discussion about her feelings and functionality at home and school is also warranted. The screening tools listed above might be helpful in this process. The patient might also benefit from starting an SSRI or participating in therapy to learn about coping skills. CBT and relaxation techniques have proved useful in such situations as well.[17]

Future Research into Pediatric Pain

With so many persistent barriers to pain control in pediatric patients, many lines of inquiry merit further attention. One important improvement would be to increase primary-care physicians' comfort with and self-efficacy in managing pain by helping them better understanding adjuvant, co-administered medications that can enhance pain control.

Given the current paucity of research, however, it is understandable that WHO's guidelines do not yet provide firm recommendations regarding the use of adjuvant medications. Still, there are many anecdotal reports of off-label medication use. For example, the use of corticosteroids as adjuvant medicines is not recommended, as there are no studies supporting their use with children, yet corticosteroids are recommended for the management of other conditions, such as in raised intracranial pressure resulting from brain tumors and in the treatment of neuropathic pain due to spinal-cord or peripheral-nerve compression.[2] Bisphonates are, likewise, presently not recommended for bone pain in children, and again, this is primarily due to a lack of evidence and to potential adverse side effects like osteonecrosis of the jaw. That said, *baclofen* (Gablofen, Kemstro) and benzodiazepines have been used for many years in managing muscle spasms and spasticity despite there being no evidence of their efficacy; WHO insists it is impossible to make recommendations for or against their use at this time.[2]

Thus, training providers in how different types of medications have been investigated to determine their potential use in pain relief for specific ailments, including bone, muscle-spasm, and neuropathic pain, could lead to significant improvements in childhood pain management. For example, some promising evidence suggests *topiramate* (Topamax) can serve as a prophylactic purpose in migraine-headache relief among children.[26]

Still, overall trials concerning the safety and efficacy of using tricyclic antidepressants, SSRIs, and SNRIs in treating children for neuropathic pain are needed; clinical experience and trial data from adult-focused studies suggest these medications have some benefit. WHO guidelines state it is impossible, at this time, to recommend *tricyclic* (TCA) and SSRI use as adjuvant medicines for neuropathic pain in children; however, there is a large body of clinical evidence that TCA amitriptyline is effective in treating children.[2, 26] Likewise, there is no current evidence to support the use of anticonvulsants in the management of childhood neuropathic pain, yet *carbamazepine* (Tegretol, Carbatrol) is commonly used for this purpose in adults and it has been used extensively and safely in childhood-seizure management. Similarly, the safety of *gabapentin* (Gralise, Neurontin) has long been established, as it is often used as an anticonvulsant for children above the age of three. While it is commonly used to treat pediatric neuropathic pain, given its overall safe profile and moderate effectiveness, no significant study has been conducted on its use with children.[2]

That said, children can necessarily benefit from integrated approaches to pain control that merge treatments known to be effective (such as those suggested by the WHO model) with non-medication-based therapies, such as psychological assessments and CBTs, as well as with adjunct medications that lessen specific kinds of pain and maximize daily functionality. Primary-care providers should be empowered to provide children with such medical care within the home.

Summary

In conclusion, childhood pain assessment and management are commonly necessary yet rarely systematically performed in pediatric-healthcare settings. Assessing pain type (acute versus chronic), severity (using validated and reliable measurement tools), and possible comorbidity with psychiatric illnesses is critical. Once type and severity are established, using a consistent method for determining which analgesic(s) and adjuvant treatment(s) ought to be considered (e.g., the WHO two-step model described above) can improve patient outcomes. Recurrent assessments for psychiatric illnesses are strongly advised. For patients with life-limiting illnesses, early referrals to pediatric palliative services will, likewise, improve quality of life.

Finally, educating providers and families about such resources, as well as improving the number of pediatric palliative-care programs available, is essential. Ideally, multidisciplinary programs incorporating therapeutic techniques like CBT could efficiently and comprehensively manage childhood pain, while also addressing common anxiety and depression comorbidities that can exacerbate pain severity. The key components of childhood pain management are multimodal, regardless of a pain's causation.

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Multiple-Choice Questions

77. A 6-year-old girl suffered a femur fracture and had her leg casted 4 days ago at her local emergency department. Her parents have subsequently brought her into your pediatric clinic for a follow-up. They are worried because she refuses to eat or drink and has voided only twice in the past 24 hours. When the girl experienced the fracture, she was discharged with a prescription for *oxycodone/paracetamol* (Percoset, Roxicet), and her mother filled the prescription, giving the patient one dose on the day of the accident. However, the following day, the mother realized she did not know if the patient's asthma medications were compatible with the prescribed analgesic and so she was reluctant to offer the patient additional pain medication. Upon examination, the patient is seen clinging to her mother, and her heart rate is 130 bpm. Her lips and mucous membranes are mildly dry. As the physician, you ask the patient if her leg hurts, and the child nods.

To enhance this child's care, clinicians should:

A. administer a dose of ibuprofen, as it has been 6 hours since she received her last dose of it.

B. use a validated tool appropriate to the child's age to assess her level of pain.

C. refer the patient to a palliative-care facility for chronic-pain management.

D. refer the patient to an orthopedics specialist for evaluation and pain control.

78. A child has been diagnosed with acute pain due to a tonsillectomy 3 days ago. He scored highly on a pain scale, and you wish to treat him according to the WHO guidelines. Clinicians should:

A. administer acetaminophen or ibuprofen only.

B. administer acetaminophen or ibuprofen, then step up quickly to codeine. If this does not quickly lessen the patient's symptoms, morphine should be administered.

C. administer acetaminophen or ibuprofen. If this does not quickly lessen the patient's symptoms, morphine should be administered.

D. ask the anesthesiologist present during the patient's procedure to manage the patient's pain.

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Best Practices in CME

Pediatric Pain Assessment and Management: A Systematic Approach Including Psychiatric Assessment

By Lindsay A. Thompson, MD, MS; Michelle Chaney-Catchpole, MD, MScPH; and Caprice Knapp, PhD

ID#: L003363

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points for easy assimilation into the clinician's armamentarium of knowledge and daily practice.

CME Lesson Overview

Pain assessment and management are common needs in pediatric healthcare that, despite many efforts, remain largely unmet. A child might present with acute pain for an intermittent issue or might have acute or chronic pain in the context of a chronic or life-limiting illness. Such situations might be further complicated if the child also has a co-occurring psychiatric illness. The aim of this lesson is to improve clinicians' understanding of how to evaluate pain type(s) and treatment(s) (e.g., medications and therapies), using a systematic approach.

Key Point 1: Key Components to Pain Management in Children

Key components to pain management in children include providing patient-level needs. Clinicians should provide anticipatory guidance about pain and its recurrence, use a standardized tool to assess pain, use a standardized tool to assess patients for psychiatric illnesses, and prescribe pain medications in accordance with measured pain levels.

Key Point 2: Pain Assessment

Key components to pain management in children include addressing patient-level needs. Clinicians should provide anticipatory guidance about pain and its recurrence by using a standardized tool to assess pain such as the *Faces Pain Scale-Revised*, the *Pieces of Hurt/Poker Chip Tool*, the *Visual Analogue Scale*, and the *Oucher Photographic and Numerical Rating Scale*.

Key Point 3: Assess for Psychiatric Illnesses

Clinicians should use a standardized tool such as the *Children's Depression Inventory*, the *Center for Epidemiological Studies' Depression Scale for Children*, the *Beck Depression Inventory*, the *Children's Depression Inventory*, and the *Pediatric Symptoms Checklist* to assess patients for psychiatric illnesses. Some scales requires a certain level of reading comprehension.

Key Point 4: Medication Treatment

Prescribe pain medications in accordance with measured pain levels. Best practice dictates to start with NSAIDs and add opioids for moderate to severe pain following the two-step approach endorsed by the World Health Organization.

Key Point 5: Practice- and System-level Needs

Providers should be educated on pain management to increase comfort with these practices among primary-care providers. Families need psychoeducation regarding medication management and advocacy for their children. Patient care should be coordinated among specialists; and patients with life-limiting conditions should be referred for palliative services early.

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