FP Essentials™

527

April 2023

Mood and Anxiety Disorders

www.aafp.org/fpe

AAFP
AMERICAN ACADEMY OF FAMILY PHYSICIANS

FP Essentials™

Barry D. Weiss, MD, FAAFP
Medical Editor

Ryan D. Kauffman, MD, FAAFP
Karl T. Rew, MD
Kate Rowland, MD, FAAFP
Associate Medical Editors

S. Lindsey Clarke, MD, FAAFP
Joel J. Heidelbaugh, MD, FAAFP, FACG
Robert C. Langan, MD, FAAFP
Brian Z. Rayala, MD, FAAFP
Editorial Board Members

Leigh Ann Backer
Editorial Director

Andrea Harden
S. Jane Thomas
Senior Associate Editors

John Moessner
Editorial Assistant

Elizabeth Jahns
Editorial Coordinator

Dave Klemm
Art Coordinator

Bret A. Taylor
Production Director

Stacey Herrmann
Production Design Manager

Bryan Colley
Randy Knittel
Senior Production Designers

Evan Palmer
Senior Digital Production Specialist

Darren Sextro
Director of Journal Media

Marilyn Harvey
Project Specialist

Susi Cordill
Circulation Manager

Rebecca Harp
Senior Circulation Strategist

Frances Spitsnogle
Circulation Specialist

R. Shawn Martin
Executive Vice President and Chief Executive Officer

Margot Savoy, MD, MPH, FAAFP
Senior Vice President of Education, Inclusiveness, and Physician Well-Being

Cover illustration by
Jonathan Dimes

ISSN# 2159-3000

FP Essentials is indexed in MEDLINE and PubMed.

Subscription Information:

American Academy of Family Physicians
11400 Tomahawk Creek Parkway, Leawood, KS 66211-2680
Phone: 800-274-2237 ▪ Email: aafp@aafp.org
Online: www.aafp.org/pubs/fpe/subscribe/subscription-management.html

Other Contact Information

Permission to reuse content: copyrights@aafp.org
Comments or suggestions for the editors: fpeeditorial@aafp.org
Proposal submissions: www.aafp.org/pubs/fpe/authors.html

527
Mood and Anxiety Disorders

Authors

Ashley Falk, MD, FAAFP
Rosa Joseph, DO, MPH
Shannon Smith, PhD, ABPP
Ashley Wilk, DO, DipABLM

Ashley Falk, MD, FAAFP, is a clinical associate professor in the department of family medicine and rural health at Florida State University (FSU) College of Medicine and a faculty member at the FSU College of Medicine Family Medicine Residency Program at BayCare Health System, Winter Haven. Dr. Falk previously served as a physician and residency faculty member in the US Air Force. In her current role, she practices the full spectrum of family medicine, including obstetrics. Her areas of interest include resident and medical student education, women's health, and mental health.

Rosa Joseph, DO, MPH, is a clinical assistant professor in the department of family medicine and rural health at FSU College of Medicine. She serves as faculty for the FSU College of Medicine Family Medicine Residency Program at BayCare Health System, Winter Haven. Dr. Joseph completed a fellowship in obstetrics and women's health. She regularly treats patients with mood and anxiety disorders and facilitates didactic trainings in mental disorders for residents. Her clinical interests include the full spectrum of family medicine.

Shannon Smith, PhD, ABPP, is a licensed psychologist in the state of Florida and is board certified in clinical psychology. She is the behavioral health faculty member and a clinical assistant professor at the FSU College of Medicine Family Medicine Residency Program at BayCare Health System, Winter Haven. Dr. Smith has extensive experience in the assessment and treatment of patients with mental health concerns in multiple settings, including private practice and university-based clinics. She is a member of the American Psychological Association (APA), Florida Psychological Association (FPA), and APA's Division 38: Society for Health Psychology.

Ashley Wilk, DO, DipABLM, is a clinical assistant professor in the department of family medicine and rural health at FSU College of Medicine. She is a founding core faculty member of the FSU College of Medicine Family Medicine Residency Program at BayCare Health System, Winter Haven, where she serves as associate program director. She also is the medical director for Winter Haven Family Health Center. Dr. Wilk's clinical interests include preventive care, osteopathic manipulative therapy, and medical education.

Disclosure: It is the policy of the AAFP that all individuals in a position to control CME content disclose any relationships with ineligible companies upon nomination/invitation of participation. Disclosure documents are reviewed for potential relevant financial relationships. If relevant financial relationships are identified, mitigation strategies are agreed to prior to confirmation of participation. Only those participants who had no relevant financial relationships or who agreed to an identified mitigation process prior to their participation were involved in this CME activity. All individuals in a position to control content for this activity have indicated they have no relevant financial relationships to disclose.

Falk A, Joseph R, Smith S, Wilk A. Mood and Anxiety Disorders. FP Essent. *2023;527:1-40.*

Copyright © 2023 American Academy of Family Physicians. All rights reserved. Written permission from the American Academy of Family Physicians is required for reproduction of this material in whole or in part in any form or medium.

Foreword

The treatment of patients with mental health conditions illustrates the best of family medicine and, too often, the worst of the US health care system. Family physicians are well-positioned to diagnose and manage these conditions.[1] Patients trust us with difficult situations and uncomfortable, confusing symptoms. We already address their preventive health needs or care for their chronic medical conditions, so it is natural that we also would provide care for their depression symptoms or new-onset panic disorder. So many physical health conditions are accompanied by mental health conditions that management of both in primary care is a reasonable approach.

At the same time, mental health care is best managed by a team. The US health care system approaches mental health care as a carve-out service. Rather than being seen as a single person needing coordinated, seamless care, sometimes a patient is treated under one set of conditions or coverage for physical health and a completely separate set of conditions or coverage for mental health. A health care system renowned for its cancer and orthopedic care may not provide mental health care at all, or may provide only psychiatric care.

The models of mental health care with the best evidence of success include fully integrated mental health and primary care, in which mental health clinicians collaborate with primary care clinicians to support one another's care of the patient. In these collaborative care models, a patient is seen as one person who needs care from multiple members of an expert team. This increases the likelihood of a good outcome for the patient and can reduce the stigma a patient may feel when undergoing an evaluation or experiencing a symptom, particularly if the patient has a history of traumatic experiences.

Unfortunately, most of us work in a fragmented environment where we refer patients to a mental health clinician, such as a social worker, psychologist, or other licensed therapist, for comanagement. Communication is hindered by incompatible health records and the need for privacy.

This edition of *FP Essentials* hopefully will strengthen your ability to care for patients with mental health conditions, even if you do not yet work in a fully collaborative care model. Section One covers the diagnosis and management of major depressive disorder. Section Two addresses bipolar disorder, and Section Three details information about suicide and suicidality. Finally, Section Four discusses generalized anxiety and panic disorders. Each section covers screening, diagnosis, and management of these common conditions.

Family physicians and primary care clinicians will care for many patients with mental health conditions. Compassion, knowledge, and an effective team will help support our work in this area. I hope you find this edition of *FP Essentials* useful in your practice.

Kate Rowland, MD, FAAFP, Associate Medical Editor
Vice Chair of Education and Associate Professor,
Department of Family Medicine
Rush University, Chicago, Illinois

1. American Academy of Family Physicians. Mental Health Care Services by Family Physicians (Position Paper). https://www.aafp.org/about/policies/all/mental-health-services.html

Learning Objectives

- Summarize the diagnosis of major depressive disorder (MDD).
- Discuss the most effective and best tolerated management options for MDD.
- Describe the tools available for bipolar disorder (BD) screening.
- Describe how to safely prescribe lithium for BD management.
- Discuss the epidemiology of suicide attempts and completions in the United States.
- Summarize effective methods of screening for suicide risk.
- Summarize the diagnosis of generalized anxiety disorder (GAD) and panic disorder.
- Discuss the most effective management options for GAD.

Contents

Pretest Questions

To assess your current knowledge of this *FP Essentials* topic, complete the pretest below and check your answers against the explanations provided at the end. Use the results to inform your study of this edition and prepare to complete the posttest, which appears later in the edition and online for CME credit. Each question has only one correct answer.

1. Which one of the following is true of major depressive disorder management?

- ☐ A. Escitalopram has been shown to be the most effective drug.
- ☐ B. Sertraline is the first-line drug for adolescents.
- ☐ C. Bupropion may not be tolerated in patients with coexisting anxiety.
- ☐ D. Bright light therapy is considered a first-line nonpharmacotherapy option.

2. When is major depressive disorder considered treatment-resistant?

- ☐ A. After treatment with a selective serotonin reuptake inhibitor (SSRI) without clinical improvement.
- ☐ B. After treatment with a selective serotonin-norepinephrine reuptake inhibitor without clinical improvement.
- ☐ C. After concurrent treatment with an SSRI and at least two augmentation therapies without clinical improvement.
- ☐ D. After treatment with two antidepressants without clinical improvement.

3. According to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision), which one of the following differentiates bipolar I from bipolar II disorder?

- ☐ A. Presence of at least one suicidal episode in the patient's lifetime.
- ☐ B. Presence of at least one manic episode in the patient's lifetime.
- ☐ C. Absence of a hypomanic episode.
- ☐ D. Absence of a depressive episode.

4. Which one of the following is considered the gold-standard mood-stabilizing drug for bipolar disorder management?

- ☐ A. Lithium.
- ☐ B. Venlafaxine.
- ☐ C. Quetiapine.
- ☐ D. Valproic acid.
- ☐ E. Trazodone.

5. Which one of the following summarizes the evidence behind the current U.S. Preventive Services Task Force (USPSTF) recommendation on screening for suicide risk in adolescents, adults, and older adults?

- ☐ A. Good quality evidence supports a benefit of screening.
- ☐ B. Moderate quality evidence supports a benefit of screening.
- ☐ C. Moderate or high quality evidence supports no net benefit of screening.
- ☐ D. Insufficient evidence to assess the harm vs benefit.

6. Esketamine is approved for management of depressive symptoms, in conjunction with an oral antidepressant, in adults with major depressive disorder and acute suicidal ideation or behavior. It has been shown to be effective in preventing suicide and reducing suicidal ideation.

- ☐ A. True.
- ☐ B. False.

7. According to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision), which one of the following defines generalized anxiety disorder?

- ☐ A. Worry in response to typical everyday stressors.
- ☐ B. Excessive anxiety and worry occurring on most days for at least 2 weeks.
- ☐ C. Excessive anxiety and worry occurring on most days for at least 3 months.
- ☐ D. Excessive anxiety and worry occurring on most days for at least 6 months.

8. Which one of the following drugs has been shown to be effective and among the best tolerated for generalized anxiety disorder management?

- ☐ A. Venlafaxine.
- ☐ B. Escitalopram.
- ☐ C. Clomipramine.
- ☐ D. Buspirone.

Pretest Answers

Question 1: The correct answer is C.
Bupropion may not be tolerated in patients with coexisting anxiety, and it is not effective for management of generalized anxiety. See page 11.

Question 2: The correct answer is D.
After an adequate trial of two antidepressants without clinical improvement, major depressive disorder is considered treatment-resistant. See page 11.

Question 3: The correct answer is B.
Per the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision), bipolar I disorder consists of recurring manic, depressive, and hypomanic episodes, with at least one manic episode required for the diagnosis. For a diagnosis of bipolar II disorder, a current or past hypomanic episode and a current or past major depressive episode are required. Additionally, a manic episode must never have occurred. See pages 13-14.

Question 4: The correct answer is A.
High-quality evidence supports the use of lithium as the gold-standard mood-stabilizing drug in patients with bipolar disorder (BD) and for BD maintenance therapy. It has been shown to reduce suicidality and manage manic and depressive episodes. See pages 16-18.

Question 5: The correct answer is D.
The 2014 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for suicide risk in adolescents, adults, and older adults concluded there is currently insufficient evidence to assess the harm vs benefit of suicide risk screening in primary care. See page 20.

Question 6: The correct answer is B.
In 2019, the Food and Drug Administration (FDA) approved esketamine nasal spray for management of depressive symptoms, in conjunction with an oral antidepressant, in adults with major depressive disorder and acute suicidal ideation or behavior. However, the prescribing information notes that the effectiveness of esketamine in preventing suicide or reducing suicidal ideation has not been shown. See page 23.

Question 7: The correct answer is D.
The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision) defines generalized anxiety disorder as excessive anxiety and worry about events or activities (eg, work, school) that occurs on most days for at least 6 months. See page 26.

Question 8: The correct answer is B.
A meta-analysis showed that duloxetine, venlafaxine, and escitalopram were more effective than placebo for generalized anxiety disorder management. Duloxetine and escitalopram were among the best tolerated. See page 27.

Key Practice Recommendations

These key learning points summarize the consensus- and evidence-based recommendations included in this edition. The sources listed here for each statement recommend that physicians perform or implement these actions directly in a clinical setting.

1. Screen for depression in the general adult population, including pregnant and postpartum women, when adequate systems are in place for accurate diagnosis, effective treatment, and appropriate follow-up

Evidence rating: SORT B
Source: U.S. Preventive Services Task Force, reference 11
Website: https://www.aafp.org/pubs/afp/issues/2016/0815/od1.html

2. Screen patients with depressive symptoms for current or past symptoms of hypomania or mania at the initial visit and at subsequent visits if there is a poor response to treatment.

Evidence rating: SORT B
Source: *Lancet*, reference 51
Website: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31544-0/fulltext

3. For patients with suicidality, document the suicide risk level and the clinical reasoning used to estimate the risk level. Document a detailed management plan to decrease suicide risk and include plans for pharmacotherapy, psychotherapy, and specialist consultations.

Evidence rating: SORT C
Source: Substance Abuse and Mental Health Services Administration, reference 87
Website: https://store.samhsa.gov/sites/default/files/sma09-4432.pdf

4. For patients with suicidality, do not use "no harm contracts" or "safety contracts," as these have not been shown to reduce suicide risk and should not be relied on to the exclusion of a formal suicide risk assessment and thorough clinical evaluation.

Evidence rating: SORT B
Sources: American Psychological Association, *J Am Acad Psychiatry Law*, references 86 and 93
Websites: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide-1410197760903.pdf; https://jaapl.org/content/jaapl/27/3/445.full.pdf

5. Prescribe a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor as a first-line drug for management of generalized anxiety and panic disorders.

Evidence rating: SORT A
Sources: *Expert Opin Pharmacother, Front Psychiatry,* references 111 and 112
Websites: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340395/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7786299/

6. Refer patients for cognitive behavioral therapy for management of generalized anxiety and panic disorders.

Evidence rating: SORT B
Sources: *BJPsych Open*, *J Consult Clin Psychol,* references 119 and 120
Websites: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6171331/; https://psycnet.apa.org/record/2007-11558-001

Strength of Recommendation Taxonomy (SORT)

Evidence Rating	Definition
A	▪ Recommendation based on consistent and good-quality patient-oriented evidence.[a]
B	▪ Recommendation based on inconsistent or limited-quality patient-oriented evidence.[a]
C	▪ Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,[a] or case series for studies of diagnosis, treatment, prevention, or screening.

[a]Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvement in patient outcomes (eg, blood pressure, blood chemistry, physiologic function, pathologic findings).

From Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy [SORT]: a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. *2004;69:548-556.*

SECTION ONE

Major Depressive Disorder

Major depressive disorder (MDD) is defined as five or more of the following symptoms in the past 2 weeks, during which at least one is depressed mood or loss of interest or pleasure: depressed mood; diminished interest or pleasure in activities; significant weight loss or gain, or decreased or increased appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; poor concentration or indecisiveness; or recurrent thoughts of death or suicidal ideation, plan, or attempt. Screening for MDD is recommended in the general adult population when resources are available for diagnosis, management, and follow-up. Several screening tools are available, including the Patient Health Questionnaire-9 (PHQ-9) and Beck Depression Inventory for Primary Care (BDI-PC). Laboratory tests may be considered to assess for significant comorbidities, differential diagnoses, or contraindications to treatment. Management of MDD depends on its severity and may include psychotherapy, pharmacotherapy, or both. The drugs most commonly used are selective serotonin reuptake inhibitors. Treatment should be continued for at least 16 to 24 weeks to prevent recurrence. Referral to a psychiatrist or other mental health clinician should be considered when the diagnosis is in question or when symptoms do not improve with standard treatment.

Case 1. SA is a 24-year-old woman who comes to your office with a 4-week history of insomnia and fatigue. When questioned, she reports the symptoms have been accompanied by depressed mood and a lack of interest in activities she once enjoyed. She also reports impaired concentration, which is affecting her job performance. She says that intense feelings of guilt have led her to think that her friends and family members would be better off without her. The physical examination results are unremarkable. The Patient Health Questionnaire-9 (PHQ-9) score is 14.

Epidemiology

The 2020 National Survey on Drug Use and Health (NSDUH) found that 8.4% of US adults had at least one major depressive episode.[1] The prevalence was higher in females than in males (10.5% vs 6.2%). The age group with the highest prevalence (17%) was adults ages 18 to 25 years.

This survey found that among US adolescents ages 12 to 17 years, 17% reported a major depressive episode in 2020.[1] Depression was more common in female adolescents than in male adolescents (25.2% vs 9.2%).[1] In children, depression typically is more common in males than in females.

In terms of racial and ethnic groups, the survey found that the prevalence of a major depressive episode was highest (15.9%) among adults who reported belonging to two or more racial or ethnic groups.[1] This effect also was seen among adolescents who reported belonging to two or more racial or ethnic groups (29.9%).

Clinical Definitions and Similar Disorders

The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision) (*DSM-5-TR*) defines a major depressive episode as a period lasting at least 2 weeks during which there is depressed mood or the loss of interest or pleasure in all or almost all activities.[2] The diagnostic criteria require five or more of the following symptoms to have been present for at least 2 weeks: depressed mood; diminished interest or pleasure in activities; significant weight loss or gain, or decreased or increased appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; poor concentration or indecisiveness; or recurrent thoughts of death or suicidal ideation, plan, or attempt. The symptoms must cause significant distress or impair function and must not be attributable to substance use or another condition.

Major depressive disorder (MDD) is defined as the presence of at least one major depressive episode occurring in the absence of a history of manic or hypomanic episodes.[2] Specifically, the *DSM-5-TR* defines MDD as five or more of the following symptoms present during a 2-week period, during which at least one of the symptoms is depressed mood or loss of interest or pleasure: depressed mood (in children and adolescents this can be irritable mood); diminished interest or pleasure in activities; significant weight loss or gain, or decreased or increased appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; poor concentration or

indecisiveness; and recurrent thoughts of death or suicidal ideation, plan, or attempt.

These symptoms must cause distress or impair function and must not be attributable to substance use or another condition.[2] Also of note, there must be absence of a manic or hypomanic episode. Mania and hypomania are periods of elevated or irritable mood, with the former considered more severe in terms of duration, intensity, and functional impairment.

Major depressive disorder may include such features as anxious distress, atypical features, melancholic features, mixed features, catatonia, peripartum onset, psychotic features, and a seasonal pattern.[2] Aspects of other conditions and disorders may mimic those of MDD, such as features of persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, and bereavement.

The current definition of persistent depressive disorder represents a consolidation of chronic MDD and dysthymia diagnoses.[2] These were previously separate diagnoses in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).[3] To meet diagnostic criteria for persistent depressive disorder, three or more of the following symptoms must be present for at least 2 years consecutively and at least one symptom must be depressed mood: depressed mood; decreased or increased appetite; insomnia or hypersomnia; low energy or fatigue; low self-esteem; poor concentration or decision-making; or feelings of hopelessness.[2]

Premenstrual dysphoric disorder consists of behavioral and emotional symptoms that impair function, begin in the week before menses onset, and improve within a few days of menses onset.[2] Substance/medication-induced depressive disorder is characterized by depressed or irritable mood or loss of interest or pleasure in most activities due to use of substances (eg, alcohol) or prescribed drugs (eg, beta blockers, corticosteroids, isotretinoin).

Bereavement is defined as the grief-related response to a death.[2] Sadness, insomnia, and poor concentration are common in MDD and bereavement; however, bereavement is characterized primarily by feelings of emptiness and loss. The intensity of bereavement tends to diminish with time, in days to weeks, but returns in waves and often is triggered by thoughts or memories. MDD symptoms are more persistent and associated with thoughts of self-loathing rather than loss.

Risk Factors

Multiple environmental, physiologic, and temperamental risk factors for MDD have been identified. Poor socioeconomic status, as defined by income, education, and occupational status, has been correlated with an increased risk of all mental conditions, including MDD.[4] Younger age, female sex, childbirth, childhood trauma, stressful life events, poor social support, serious illness, dementia, and substance use disorder have been shown to increase the risk of MDD.[5] The annual prevalence of MDD in patients with a chronic illness is 25%.[6] People with negative affectivity, a personality trait associated with the tendency to experience negative emotions, are more likely than others to develop MDD in response to stressful events.[2]

Social factors have been shown to affect MDD development. Lesbian, gay, and bisexual people are more than 3 times as likely as heterosexual people to experience an episode of MDD.[7] The prevalence of MDD is higher among adults who are single, divorced, or widowed than among those who are married or cohabitating.[5]

Genetic risk factors also have been found. First-degree relatives of individuals with MDD have an increased risk of developing MDD.[2] Heritability based on twin studies has been estimated at 37%.[8]

Racial risk factors likely reflect a combination of socioeconomic and cultural factors and health disparities. Among different racial and ethnic groups, Native American people have the highest prevalence of MDD (16%) and Asian/Pacific Islander people the lowest (7%).[5]

Protective factors include personal attributes such as the ability to cope with stress and adversity and problem-solving skills.[9] The ability to confide in others and membership in a sport club or gym are associated with a lower risk of MDD. Engagement in physical activity appears to be protective. The exact type, duration, and frequency of protective physical activity are not clear, but some benefits of even minimal activity have been shown.[10]

Screening

The U.S. Preventive Services Task Force (USPSTF) recommends screening for depression in the general adult population, including in pregnant and postpartum women.[11] It advises that screening be implemented with adequate systems in place for accurate diagnosis, effective treatment, and appropriate follow-up.

The USPSTF recommends screening for MDD in adolescents ages 12 to 18 years.[12] However, it found insufficient evidence to assess the benefits vs harms of screening for MDD in children 11 years and younger. The American Academy of Pediatrics (AAP) and the American Psychiatric Association support the Guidelines for Adolescent Depression in Primary Care (GLAD-PC), which recommend screening for depression in adolescents 12 years and older.

Screening tools used in primary care have reasonable sensitivity and specificity for detection of MDD (*Table 1*). They typically are brief and self-administered by the

TABLE 1
Screening Tools for Major Depressive Disorder, Generalized Anxiety Disorder, and Panic Disorder

Screening Tool	Sensitivity (%)	Specificity (%)	Age Group (Years)
Major Depressive Disorder			
Patient Health Questionnaire-9 (PHQ-9)	88	85	18 and older
Patient Health Questionnaire-2 (PHQ-2)	76	87	18 and older
Beck Depression Inventory (BDI)	97	99	18 and older
The World Health Organization-5 Well-Being Index (WHO-5)	93	64	18 and older
Patient Health Questionnaire–Adolescents (PHQ-A)	89.5	75.5	12-17
Edinburgh Postnatal Depression Scale (EPDS)	81	88	18 and older
Geriatric Depression Scale (GDS)	79	67	65 and older
Generalized Anxiety Disorder			
Generalized Anxiety Disorder (GAD-7) scale	89	83	18 and older
Panic Disorder			
Panic Disorder Severity Scale (PDSS)	83.3	64	18 and older
Patient Health Questionnaire–Panic Disorder (PHQ-PD)	81	99	18 and older

Information from various sources.

patient. These tools include the Patient Health Questionnaire-9 (PHQ-9) (*Figure 1*), Patient Health Questionnaire-2 (PHQ-2), Beck Depression Inventory for Primary Care (BDI-PC), and World Health Organization-5 Well-Being Index (WHO-5). The PHQ-9 modified for Adolescents (PHQ-A) can be used to screen patients ages 12 to 17 years.[13] The Geriatric Depression Scale (GDS) is a specific screening tool for patients 65 years and older.

A 2019 meta-analysis showed that a cutoff PHQ-9 score of 10 was 88% sensitive and 85% specific for detection of MDD in adults.[11] The PHQ-2 is an abbreviated form of the PHQ-9 and can be used to quickly evaluate for depressed mood and anhedonia.

When a screening result is positive, it should be followed by a detailed history and evaluation to determine whether the patient meets diagnostic criteria for MDD.[14] Other possible causes of symptoms should be ruled out.

Symptoms

Patient age and culture can affect manifestation of MDD symptoms. Adults exhibit depressed mood or loss of interest in usual activities.[2] Children may have difficulty characterizing their emotions and exhibit an irritable mood. In older adults, memory difficulties may be the primary symptom of MDD, which can be mistaken for an early sign of dementia. Social isolation, anger, crying, diffuse pain, and other somatic symptoms may be more commonly associated with depression across cultural contexts.

Symptoms also vary depending on associated features. Patients with MDD with atypical features have mood reactivity (eg, mood brightens in response to positive events) and two or more of the following: significant weight gain or increased appetite; hypersomnia; leaden paralysis; or interpersonal rejection sensitivity.[2] Patients with MDD with psychotic features experience delusions and/or hallucinations during the depressive episode.

Diagnostic Evaluation

Major depressive disorder is a clinical diagnosis. As such, there are no specific recommendations for laboratory tests in patients with suspected MDD. However, laboratory tests may be considered to assess for significant

Name_____ Date _____

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

(For office coding: Total Score _____ = _____ + _____ + _____)

If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Figure 1 . Nine-Symptom Checklist (Patient Health Questionnaire-9)

Scoring: 1-4 points: minimal depression; 5-9 points: mild depression; 10-14 points: moderate depression; 15-19 points: moderately severe depression; 20-27 points: severe depression.

Reprinted from Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. *2001;16(9):606-613.*

comorbidities, differential diagnoses, or contraindications to treatment. Tests may be warranted when findings on the history or evaluation appear incongruent with MDD, when a patient presents with severe symptoms or psychotic features, or in cases of treatment-resistant depression.

Initial laboratory tests may include a complete blood cell count, complete metabolic panel, and thyrotropin, vitamin B_{12}, and folate levels.[14] In patients with chronic conditions or a history of substance abuse and in older adult patients, additional tests may be warranted. Other tests to consider are liver function tests, testosterone level (in men), Lyme titer, rapid plasma reagin test, HIV test, and urine and serum toxicology screening.

Neuroimaging is indicated only when the history and physical examination suggest the possibility of structural brain disease. Biomarkers continue to be studied in the diagnosis of MDD but are not part of standard practice. Elevations in C-reactive protein, tumor necrosis factor, and interleukin 6 levels, among other markers of inflammation, have been seen in patients with depression.[14,15]

Management

The effectiveness of MDD management can be measured by improvement in and resolution of symptoms. The mainstays of treatment are psychotherapy, pharmacotherapy, or a combination of both.[16]

Randomized trials have shown benefits of psychotherapy and pharmacotherapy in MDD management. Psychotherapy is the recommended first-line therapy for mild depression.[17] Psychotherapy and pharmacotherapy have been shown to be equally effective in management of moderate to severe depressive disorders, including MDD, so either

is a reasonable choice for first-line therapy.[18] Management with a combination of psychotherapy and pharmacotherapy has been shown to be more effective than either alone.[16,18] The clinician can consider use of combination therapy at the time of initial diagnosis.

For adult patients, the American Psychological Association recommends psychotherapy or a second-generation antidepressant for initial treatment of depression, including MDD.[19] Psychotherapy can consist of behavioral therapy, cognitive behavioral therapy, interpersonal psychotherapy, psychodynamic therapies, or supportive therapy. If combination therapy is being considered, cognitive behavioral therapy or interpersonal psychotherapy plus a second-generation antidepressant are recommended.

PHARMACOTHERAPY

Second-generation antidepressants include selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs).[19] Other drugs used for MDD management include atypical antidepressants, serotonin modulators, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).[16] Because of their effectiveness and tolerability, SSRIs often are used as first-line drugs. They are the most commonly prescribed class of antidepressants in the United States.[20]

Escitalopram and sertraline frequently are used for initial pharmacotherapy for acute major depression in adults because of their efficacy, acceptability, and cost.[21] A 2021 systematic review showed amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine to be the most effective drugs for MDD management.[22] This review found that citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more well-tolerated than other drugs.

Bupropion, a norepinephrine-dopamine reuptake inhibitor, can be considered for patients who are concerned about sexual dysfunction or interested in smoking cessation.[23] Because of its activating effects, this drug may not be tolerated in patients with coexisting anxiety, and it is not effective for management of generalized anxiety. It also is not as effective as most SSRIs for management of major depression symptoms.[21]

Tricyclic antidepressants and MAOIs often are avoided because of safety concerns and adverse effects. These drugs typically are reserved for patients who have not benefited from other therapies.[23] TCAs have anticholinergic properties and can cause drowsiness, constipation, postural hypotension, and urinary retention. Their use generally is avoided in elderly patients. TCAs also are associated with a risk of lethal overdose. Use of MAOIs requires dietary restriction of foods containing tyramine. These drugs also have many adverse effects (eg, dizziness, dry mouth).

There is little evidence of greater effectiveness of one antidepressant drug over another. Therefore, drug selection should be based on patient preference, tolerability, cost, comorbidities, and possible adverse effects.[23] If a first-degree relative of the patient has been treated effectively with a particular antidepressant, that drug may be more effective for the patient than others.

Improvement in MDD symptoms with pharmacotherapy typically can be observed in 4 to 6 weeks.[24] Antidepressant therapy should be continued for at least 16 to 24 weeks to prevent recurrence.[25] If improvement is not seen, reassessment of the drug and/or adjustment of the dosage should be considered. Switching to another SSRI, SNRI, atypical antidepressant, or serotonin modulator is recommended.[24]

After an adequate trial of two antidepressants without clinical improvement, MDD is considered treatment-resistant. Augmentation therapy should be considered next for these patients.[24] The drugs most commonly used and studied for augmentation therapy include atypical antipsychotics, thyroid hormone, and lithium. Addition of a second antidepressant also is an option. Aripiprazole, lithium, olanzapine, quetiapine, risperidone, and thyroid hormone have been found to be similarly effective for augmentation therapy.

Esketamine (Spravato), a derivative of ketamine, recently has been approved by the Food and Drug Administration (FDA) for management of treatment-resistant depression in conjunction with an oral antidepressant.[26] Its effectiveness has been shown in short-term studies, and it is available as a nasal spray. Adverse effects include dizziness, elevated blood pressure, and feelings of dissociation.

Case 1, cont'd. After ruling out substance use and other conditions as possible causes of SA's symptoms, you diagnose major depressive disorder. After a shared decision-making discussion, you refer her for cognitive behavioral therapy and prescribe escitalopram 10 mg/day.

In adolescents. For initial treatment of depressive disorders in adolescents, including MDD, the American Psychological Association recommends either psychotherapy (ie, cognitive behavioral therapy, interpersonal psychotherapy) or fluoxetine as a first-line drug.[19] It found insufficient evidence to recommend one of these over the other. Other drugs that may be considered for initial pharmacotherapy include sertraline, escitalopram, and duloxetine.[27] Clinicians should counsel patients and family members on the possible increased risk of suicidality when initiating drug therapy. As in adults, psychotherapy should be considered as part of the management plan for adolescents with MDD.

In pregnant patients. Management of antenatal and postpartum depressive disorders is challenging because all

drugs used to manage MDD cross the placenta and can be detected in breast milk.[28] Sertraline, fluoxetine, duloxetine, and bupropion have been studied most widely in pregnant patients. Although studies have shown that the risks of teratogenicity and neonatal abstinence syndrome with these drugs are low, these risks should be discussed with patients.

INTEGRATIVE MEDICINE THERAPIES

Herbal therapies have been studied for MDD management, including St. John's wort (*Hypericum perforatum*). In studies, when used as monotherapy for mild and moderate depression, it has been shown to be more effective than placebo.[29] However, evidence of study heterogeneity and a lack of research on its use in severe depression reduce the quality of the evidence. St. John's wort interacts with multiple drugs, including some that commonly are prescribed in primary care (eg, oral contraceptives, omeprazole, warfarin). St. John's wort may inhibit the reuptake of serotonin and can lead to an increased risk of serotonin syndrome when used in combination with SSRIs.

Although they currently are used predominantly in research settings, psychedelics also have been used to manage MDD. The drugs studied include psilocybin, 3,4-methylenedioxymethaomphetamine (MDMA), *N,N*-dimethyltryptamine (DMT), and lysergic acid diethylamide (LSD).[30] One study showed that psilocybin is as effective as escitalopram for depression management.[31] A systematic review found that psychedelics may be used as a novel method of managing depression in the future.[30]

OTHER THERAPIES

Electroconvulsive therapy (ECT) is an initial treatment option that has been shown to be effective for MDD.[23] ECT has an immediate onset of action, which makes it ideal for patients with suicidal ideation or other life-threatening behaviors. ECT has been used for management of severe and treatment-resistant depression for approximately 80 years.[23,32] Although it is effective, ECT often remains a last resort option because of its adverse effects, which include headache, nausea, myalgia, and confusion.[32] Retrograde amnesia may occur but typically is self-limited.

Transcranial magnetic stimulation (TMS) involves placement of an electromagnetic coil against the scalp to induce electrical currents in the cerebral cortex.[23] Evidence supports the clinical efficacy of TMS as an antidepressant and a therapy for treatment-resistant depression. Placement is an outpatient procedure that does not require anesthesia. Patients typically receive daily 30-minute sessions for 2 to 6 weeks. The need for frequent office visits may limit patient adherence. Adverse effects are infrequent but may include headache and scalp discomfort.

Exercise has been studied as an adjunct treatment for MDD. Studies have shown exercise to be effective as monotherapy and augmentation therapy.[10] As a result, exercise is now included in the American Psychiatric Association management recommendations for MDD.[23]

The American Psychological Association suggests exercise monotherapy or St. John's wort monotherapy for adults with depression for whom psychotherapy or pharmacotherapy is ineffective or unacceptable.[19] If neither of these monotherapies is acceptable or available, the guidelines suggest consideration of bright light therapy or yoga. They note that there is insufficient evidence to recommend tai chi, acupuncture monotherapy, omega-3 fatty acids monotherapy, or *S*-adenosyl-L-methionine (SAMe).

Referral

Referral to a psychiatrist or other mental health clinician should be considered when the family medicine physician does not have the training to provide the recommended treatment, when questions exist about accuracy of the diagnosis, or when the condition does not improve with available treatments.

Case 1, cont'd. SA returns to your office 4 weeks later for a follow-up visit. She is adhering to psychotherapy and pharmacotherapy and reports moderate symptom improvement. You readminister the PHQ-9, and the score improved from 14 to 10 points. You and SA agree to increase the escitalopram dosage to 20 mg/day. At another follow-up visit 4 weeks later, she reports complete resolution of her symptoms. Because of the risk of recurrence, she plans to continue taking escitalopram for the next 24 weeks.

SECTION TWO

Bipolar Disorder

Bipolar I disorder affects approximately 0.4% to 1% of the global population. In the United States, bipolar-related disorders are associated with a significant economic burden because of the functional impairment they cause. Due to long wait times for access to specialist physicians and insurance issues, primary care physicians frequently manage this condition. Up to 4% of patients in primary care have bipolar disorder (BD). The diagnostic criteria for bipolar-related disorders are complex, and screening tools alone are insufficient for identification. Diagnosis involves a comprehensive clinical assessment that often requires multiple visits. Lithium continues to be the gold-standard mood-stabilizing drug for BD management and maintenance therapy in adults. Some anticonvulsants and atypical antipsychotics also have been shown to be effective for maintenance therapy. Ketamine is being studied as a possible future treatment option, but current research does not support its use. Psychotherapy, such as cognitive behavioral therapy and psychoeducation on management strategies, can be a useful adjunct therapy. Mental health clinicians can support primary care physicians in the evaluation and treatment of patients with BD.

Case 2. CV is a 22-year-old man who comes to your office for a follow-up visit for depression management. He has a history of feeling depressed most of the day, anhedonia, poor appetite, significant weight loss without dieting, passive suicidal ideation, and feelings of worthlessness. As a result, he withdrew from his college classes this semester.

At the last appointment, you prescribed escitalopram. CV says that shortly after starting this drug, he could not sleep for several days, felt more energetic than usual, was easily distracted, and spent significantly more money than usual shopping online. He stopped taking the escitalopram but these symptoms continued. CV has no history of substance use. He denies any psychotic symptoms.

Epidemiology

Bipolar-related disorders are characterized by significant changes in mood and a cyclic pattern of depressive and manic/hypomanic episodes. Bipolar I disorder affects approximately 0.4% to 1.0% of the global population.[33] In the United States, it causes a significant economic burden of approximately $195 billion.[34] Direct medical costs account for one-quarter of this amount and indirect costs (eg, reduced productivity) account for the remainder.

People with bipolar disorder (BD) have a significantly higher mortality rate than people in the general population, partially because of a higher rate of suicide.[35] The suicide rate is 20 times higher in adults with BD than in adults in the general population. The rate is 50 times higher in children and adolescents with BD than in their peers in the general population. Between 34% and 50% of adults with BD attempt suicide at least once in their lifetimes; between 15% and 20% complete suicide.[36]

Because of long wait times for access to specialist physicians and insurance issues, primary care physicians frequently treat patients with BD.[37,38,39] Up to 4% of primary care patients have BD.[39] Primary care physicians serve an important role in providing treatment for these patients.[40]

Clinical Definitions

Bipolar and related disorders are grouped as a class of mood disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision) (*DSM-5-TR*).[2] They involve mood instability, including a combination of depressive and manic/hypomanic episodes.

Per the *DSM-5-TR*, bipolar I disorder consists of recurring manic, depressive, and hypomanic episodes, with at least one manic episode required for the diagnosis.[2] A manic episode is defined as a period of abnormal elevated, expansive, or irritable mood and increased activity or energy lasting 1 week. During this period, three or more of the following symptoms (four if the mood is irritable) must be present: inflated self-esteem or grandiosity; decreased need for sleep; increased talkativeness or pressured speech; flight of ideas or racing thoughts; distractibility; increased goal-directed activity or psychomotor agitation; or excessive involvement in activities with potential serious consequences (eg, shopping sprees, sexual activity). The condition must impair functioning, require hospitalization to prevent harm to the self or others, or include psychotic features. It must not be due to substance use or another condition.

For a diagnosis of bipolar II disorder, a current or past hypomanic episode and a current or past major depressive episode are required.[2] Additionally, a manic episode must

never have occurred. The hypomanic episode and major depressive episode must not be better explained by schizoaffective disorder or superimposed on a schizophrenic, delusional, or other psychotic disorder. Symptoms of depression or unpredictable mood must cause distress or functional impairment.

A hypomanic episode is defined as a period of elevated, expansive, or irritable mood and increased activity or energy lasting at least 4 days.[2] During this period, three or more of the following symptoms must persist (four if the mood is irritable): inflated self-esteem or grandiosity; decreased need for sleep; increased talkativeness or pressured speech; flight of ideas or racing thoughts; distractibility; increased goal-directed activity or psychomotor agitation; or excessive involvement in activities with serious potential consequences. The hypomanic episode must represent a change in functioning, be uncharacteristic of the patient, and be observable by others. It must not be severe enough to cause impairment and not be due to substance use or another condition.

Risk Factors

Research consistently has shown genetics to be a factor in BD, with twin studies finding a monozygotic concordance ranging from 40% to 70%.[41] Patients with a first-degree relative with BD have a 5% to 10% lifetime risk of developing the disorder.

Environmental factors, such as childhood trauma, parental history of BD, and recent life stress are associated with early onset and poorer prognosis.[2,41] Misuse of a wide range of substances (eg, cannabis, cocaine, alcohol) has been associated with manic symptoms and initial symptom onset.[2,42] Various conditions are seen more commonly in patients with BP, including asthma,[41,43,44] irritable bowel syndrome,[41,45] obesity,[41,46] migraine,[41,47] traumatic brain injury,[41,48] and multiple sclerosis.[41,49]

Screening

The timeliness of detection, evaluation, and diagnosis is key to a patient's prognosis and risk of recurrence. One study found that patients who received treatment early in the course of BD had higher response rates than patients who received treatment later.[50] In addition, patients with a history of fewer episodes who received treatment during the maintenance phase had reduced rates of manic episode recurrence. Early detection and management are imperative for effective treatment and to decrease the risk of manic episode recurrence.

Clinicians should screen patients who present with depressive symptoms for current or a past history of hypomania or mania at the initial visit and at subsequent visits if there is a poor response to treatment.[51] These patients may have undiagnosed BD or develop BD. One study estimated the rate of diagnosis change from major depression to BD, due to inaccurate initial diagnosis or manifestation of new symptoms, at 1.25% per year. Other studies have estimated the rate of change to be 20% to 30% in the first 3 years after first diagnosis. Thus, regular assessment for new symptoms of BD should occur in patients with a history of depressive symptoms.

One of the most frequently used screening tools is the Mood Disorder Questionnaire (MDQ) (*Table 2*), which has a sensitivity of 80% and specificity of 70% for BD.[51] The Hypomania Checklist 32 (HCL-32) also can be used for screening purposes. It has a sensitivity of 82% and specificity of 57%. These tools are designed for screening only. They may yield false-positive results, so positive results warrant a thorough assessment to establish a diagnosis. The *DSM-5-TR* mentions the Altman Self-Rating Mania Scale (ASRM) as an emerging screening tool for mania that requires further study.[2]

Diagnosis

Bipolar disorder is diagnosed after a comprehensive clinical assessment.[51] Supplemental information such as that provided by a family member or close friend can assist with diagnostic clarity. The use of mood diaries and other corroborative data can help in determining a diagnosis. Given the complexities of BD, establishing a new diagnosis at an initial visit can be challenging; therefore, assessment of patients with this disorder may require multiple visits.

The duration, intensity, and frequency of depressive, manic, and hypomanic episodes guide diagnostic evaluation and management.[2] Specifically, duration of manic symptoms is one of the main factors that differentiates manic and hypomanic episodes. A manic episode requires symptoms that persist for at least 1 week. For a hypomanic episode, symptoms must occur for at least 4 consecutive days. The level of impairment is the other distinguishing factor. A hypomanic episode does not cause significant impairment in functioning.

Distinguishing between a manic and hypomanic episode directly influences the diagnosis.[2] The presence of at least one manic episode in a patient's lifetime yields a diagnosis of bipolar I disorder, whereas the presence of only hypomanic episodes results in a diagnosis of bipolar II disorder. For patients with no history of manic or hypomanic symptoms or episodes, diagnosis of a depressive disorder may be accurate.

Other bipolar-related disorders as categorized by the *DSM-5-TR* are cyclothymic disorder, substance/medication-induced bipolar and related disorder, and bipolar and

TABLE 2
Mood Disorder Questionnaire

1. Has there ever been a period of time when you were not your usual self and...		
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	Yes	No
...you were so irritable that you shouted at people or started fights or arguments?	Yes	No
...you felt much more self-confident than usual?	Yes	No
...you got much less sleep than usual and found you did not really miss it?	Yes	No
...you were much more talkative or spoke much faster than usual?	Yes	No
...thoughts raced through your head or you could not slow your mind down?	Yes	No
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	Yes	No
...you had so much more energy than usual?	Yes	No
...you were much more active and did many more things than usual?	Yes	No
...you were much more social or outgoing than usual (eg, you telephoned friends in the middle of the night)?	Yes	No
...you were much more interested in sex than usual?	Yes	No
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	Yes	No
...spending money got you or your family into trouble?	Yes	No
2. If you answered "Yes" to more than one of the above, have several of these ever happened during the same period of time?	Yes	No

3. How much of a problem did any of these cause you (eg, being unable to work; having family, money, or legal troubles; getting into arguments or fights)? *Please circle one response only.*	No problem	Minor problem	Moderate problem	Serious problem

4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	Yes	No
5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?	Yes	No

Scoring:

All three of the following criteria must be met for a positive screening result:

Answered "Yes" to 7 or more of the 13 items in question number 1;

AND

Answered "Yes" to question number 2;

AND

Answered "Moderate problem" or "Serious problem" to question number 3

A positive result should be followed by a comprehensive evaluation for bipolar-related disorders

Adapted from Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry. *2000;157(11):1873-1875.*

related disorder due to another medical condition.[2] Additional diagnoses exist for patients who do not meet the full diagnostic criteria, but have bipolar-related symptoms with functional impairment. These include other specified bipolar and related disorder and unspecified bipolar and related disorder.

Other specified bipolar and related disorder is used for patients with symptoms characteristic of BD that cause

functional impairment, but do not meet the diagnostic threshold for BD.[2] The *DSM-5-TR* offers five examples of these types of presentations. These include: short-duration hypomanic episodes (2-3 days) and major depressive episodes; hypomanic episodes with insufficient symptoms and major depressive episodes; hypomanic episode without a previous major depressive episode; short-duration cyclothymia (less than 24 months); and manic episode superimposed on a schizophrenic, delusional, or psychotic disorder.

In settings and situations in which information is limited and insufficient to make a precise diagnosis, such as in the emergency department, a diagnosis of unspecified bipolar and related disorder can be used to describe symptoms characteristic of BD.[2]

Case 2, cont'd. On the Mood Disorder Questionnaire, CV answers "yes" to 8 of the 13 items and indicates that the symptoms have caused "no problem" in his functioning. On further interviewing, he states that the symptoms lasted for 5 consecutive days. Because of the manic symptoms lasting at least 4 days, you diagnose a hypomanic episode. CV denies any episodes lasting at least 1 week. Given the history of a hypomanic episode and at least one depressive episode, CV meets the diagnostic criteria for bipolar II disorder.

Laboratory Tests

Laboratory tests are not used for BD diagnosis, but can be useful for assessing somatic functioning, establishing baseline measurements for pharmacotherapy, and evaluating for a differential diagnosis. A complete blood cell count can be helpful when considering anticonvulsant treatment.[52,53] A basic metabolic panel is useful in assessing liver and kidney function, which are important for patients taking lithium, anticonvulsants, or antidepressants. A fasting blood glucose level can establish a baseline for patients taking drugs that may cause hyperglycemia or weight gain. A urine pregnancy test can help prevent use of potentially teratogenic drugs.

An electrocardiogram can be considered in patients older than 40 years.[53] This can provide baseline measurements for patients taking high-risk drugs, such as lithium and some antipsychotics. A cardiovascular disease risk screening including a lipid profile also can help establish baselines.[52,53] Some drugs for BD management can adversely affect cardiovascular risk status. Finally, a urine toxicology screen can determine whether substance use is contributing to symptoms.

Management

Management goals for patients with BD are individualized and may include: prevention and management of manic, hypomanic, and depressive symptoms; normalization of the sleep cycle; a decrease in suicidal behaviors; improvement in overall well-being; improvement in cognitive functioning; and prevention and management of comorbid conditions.[51]

PHARMACOTHERAPY

Pharmacotherapy is foundational to BD management.[51] The Food and Drug Administration (FDA) has approved multiple psychotropic drugs for this indication. These drugs can be categorized into three types: salts, atypical antipsychotics, and anticonvulsants. *Table 3* outlines the current FDA-approved drugs and specifies the indication for each (eg, mania, maintenance, depression). Drug therapy typically should be continued indefinitely after an effective and tolerated treatment has been identified.

A 2020 study examined the 20-year prescribing trends of outpatient psychiatrists.[54] It showed increased use of antipsychotics from 1997-2000 and 2013-2016, respectively (12.4% to 51.4%), decreased use of mood stabilizers (62.3% to 26.4%), and increased use of antidepressants without a mood stabilizer (17.9% to 40.9%).

A meta-analysis found differences in the efficacy profiles of various drugs during maintenance treatment.[55] It showed the effectiveness of lithium, divalproex, aripiprazole, olanzapine, quetiapine, and risperidone in prevention of depressive or manic/mixed recurrences. However, the study found that monotherapy did not significantly reduce the risk of depressive and manic/mixed episodes. Among combination therapies, it found that risperidone plus lithium or divalproex, as well as ziprasidone plus lithium or divalproex, were effective in reducing manic episodes. In contrast, quetiapine plus lithium or divalproex were effective in reducing manic/mixed episodes and depressive episodes.

The use of antidepressants for patients with BD is controversial because of significant variation in patient response and the possibility of inducing mania.[54] It has been shown that tricyclic antidepressants are more likely to induce a manic episode than selective serotonin reuptake inhibitors or buproprion.[56] Antidepressants as monotherapy for mania, BD, or mixed episodes are known to be ineffective and may induce manic episodes.[51] However, approximately one-third of patients diagnosed with BD in the primary care setting receive antidepressants.[57]

A 2020 cohort analysis found that rates of antidepressant prescribing may be related to patients spending more time in a depressive vs manic phase, refractoriness to treatment, and ineffectiveness or lack of tolerability of other previously used types of drugs.[54] For most patients with BD, antidepressants should be used as an adjunct to mood stabilizers.[51]

Lithium. High-quality evidence supports the use of lithium as the gold-standard mood-stabilizing drug in

TABLE 3
FDA-Approved Drugs for Bipolar Disorder Management

Drug Class	Drug	Common Adverse Effects	Mania	Mixed Episode	Maintenance	Depression
Salts	Lithium	Hyperparathyroidism, hypothyroidism, weight gain, nausea, dizziness	X		X	
Atypical antipsychotics	Aripiprazole	Weight gain, constipation, nausea, dizziness, headache	X	X	X	
	Asenapine	Orthostatic hypotension, seizure, suicidal thoughts, weight gain, neuroleptic malignant syndrome	X	X		
	Cariprazine	Indigestion, vomiting, akathisia, extrapyramidal sign, somnolence	X	X		
	Lurasidone	Hyperglycemia, weight gain, diarrhea, nausea, vomiting				X
	Olanzapine	Orthostatic hypotension, hypercholesterolemia, hyperglycemia, elevated serum triglyceride levels, weight gain, dizziness	X	X	X	
	Olanzapine-fluoxetine	Orthostatic hypotension, hypercholesterolemia, hyperglycemia, weight gain, blurred vision				X
	Quetiapine	Elevated diastolic and systolic arterial pressure levels, orthostatic hypotension, tachycardia, weight gain, dizziness	X			X
	Risperidone	Rash, weight gain, upper abdominal pain, dizziness, upper respiratory tract infection	X	X		
	Ziprasidone	Rash, weight changes, nausea, dizziness, headache	X	X		
Anticonvulsants	Carbamazepine	Hypotension, rash, nausea, dizziness, blurred vision	X	X		
	Lamotrigine	Rash, abdominal pain, nausea, dizziness, headache			X	
	Valproic acid	Abdominal pain, nausea, dizziness, headache, blurred vision	X			

FDA = Food and Drug Administration.

Information from Butler M, Urosevic S, Desai P, et al. Treatment for bipolar disorder in adults: a systematic review. Agency for Healthcare Research and Quality*; 2018. https://www.ncbi.nlm.nih.gov/books/NBK532183/; Clinical Key. ClinicalPharmacology.com. https://www.clinicalkey.com/pharmacology/*

patients with BD and for BD maintenance therapy.[51,53] It has been shown to reduce suicidality and manage manic and depressive episodes.[51]

The recommended initial dosage is 300 mg 2 times/day, and this can be titrated every 2 to 3 days as tolerated until a therapeutic dosage is achieved.[53] A serum lithium level of 0.6 to 1.5 mEq/L is recommended. The target dosage for lithium is 900 to 1,800 mg/day; however, some patients may experience therapeutic benefit with lower dosages.

Patients taking lithium must regularly undergo laboratory tests and schedule follow-up visits.[53] Clinicians should monitor these patients for effects of lithium toxicity, such as acute kidney injury. Lithium can cause a range of adverse effects, including diabetes insipidus, sedation, cognitive impairment, tremor, and weight gain.[51]

Anticonvulsants, atypical antipsychotics, and antidepressants. High-quality evidence also supports the use of lamotrigine, quetiapine, quetiapine in combination with lithium or valproic acid, aripiprazole, and olanzapine for BD maintenance therapy.[53] Each drug has advantages and disadvantages. Because of the likelihood of inducing a manic episode, trazodone, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors should be avoided.[52]

Adverse drug effects. Clinicians must be familiar with the common adverse effects associated with drugs used to manage BD. These are listed in *Table 3*.

PSYCHOTHERAPY

Psychotherapy as an adjunct to pharmacotherapy has been shown to decrease hospitalization and recurrence rates, improve functioning, and reduce the need for drugs.[53,58] Cognitive behavioral therapy, family and conjoint therapy, and interpersonal therapy can help stabilize depressive symptoms.[58] In addition, psychoeducation on management strategies targeted at BD delivered in group and family formats has been shown to be beneficial.

ADDITIONAL THERAPIES

Evidence supports the use of electroconvulsive therapy for patients with psychotic depression and mania.[53] Regular exercise, caregiver support, and a well-balanced diet can be helpful for patients with BD.[59] There is insufficient evidence to support use of light therapy and omega-3 fatty acid supplements as adjunctive therapies.[60,61] Research has been increasing on the use of ketamine for management of psychiatric disorders, including bipolar-related disorders, but there currently is no consistent, high-quality evidence to support its use.[62]

Case 2, cont'd. Because CV now has a diagnosis of bipolar II disorder, you discontinue the escitalopram, provide a 1-month prescription for lithium, and refer him to a psychiatrist for psychotherapy. You tell CV that if he experiences difficulty establishing care with the psychiatrist, you are prepared to continue treatment.

Treatment Effectiveness, Recurrence, and Prognosis

According to the *DSM-5-TR*, more than 90% of patients who have experienced a manic episode will experience additional mood episodes (manic, hypomanic, and/or depressive).[2] Results from a meta-analysis of 38 studies found that patients who received pharmacotherapy for BD (eg, lithium, quetiapine, valproate) had significantly lower rates of recurrence of any mood episode compared with patients who received placebo.[63] Completed suicide and mortality rates also were lower for patients who received pharmacotherapy.

Research has suggested multiple precipitating factors for manic and hypomanic episodes, including increased goal-directed behaviors, disruption in sleep routines, spring and summer seasonal changes, antidepressant drugs, difficult life events, and elevated levels of emotional expression.[64] Warning signs of recurrence include sleep impairment, agitation, and increased goal-directed activity.

Effective management can improve the short-term prognosis for patients with BD. However, the long-term prognosis for these patients is poor regardless of management.[51] Recurrence rates are estimated to be 40% to 60% in the first 24 months post hospital discharge after a first manic episode, and less than 50% of patients experience a complete functional and symptomatic recovery after a first manic episode.

SECTION THREE

Suicide

In the United States, suicide was the cause of more than 47,500 deaths in 2019. Females attempt suicide 1.5 times more frequently than males. However, rates of completed suicide are higher in males than in females. In the US population, the suicide rate is highest in adults older than 75 years. Factors associated with an increased risk of suicide include geographic and social isolation, low access to clinical resources, unemployment, and poverty. Patients with mental disorders, including schizophrenia, major depressive disorder (MDD), bipolar disorder, and substance use disorder, are at increased risk. Directly questioning a patient about suicide has not been shown to increase the patient's risk of completing suicide. Physicians should ask patients about any suicide plans and details of timing, location, means, and any preparation for the act. The goal of pharmacotherapy in patients with suicidality is management of comorbid mood disorders, most often MDD. Esketamine nasal spray is a pharmacotherapy option for MDD management in patients with acute suicidal ideation or behavior. It is approved for use in conjunction with an oral antidepressant. Use of "no harm contracts" or "safety contracts," in which patients attest that they will not commit suicide, should not be relied on to the exclusion of a formal suicide risk assessment and thorough clinical evaluation.

Case 3. ZT is a 28-year-old transgender man who comes to your office for evaluation of urinary tract infection (UTI) symptoms. He has a history of anorexia nervosa. When you enter the room, he makes little eye contact. After addressing the UTI symptoms, you ask ZT how else you can help him today. ZT responds, "I don't know if you can. My life is not worth living anymore and I need to end this pain."

Epidemiology

Among all age groups in the United States, suicide was the tenth leading cause of death in 2019, and the cause of more than 47,500 US deaths.[65,66] There were an estimated 1.4 million suicide attempts that year.[67,68] This number equates to suicide attempts by approximately 0.5% of Americans 18 years or older.[67] In 2015, approximately 575,000 people visited a hospital because of injuries from self-harm. The 2018 National Survey on Drug Use and Health (NSDUH) found that females attempted suicide 1.5 times more frequently than males.[69] However, rates of completed suicide were higher in males than in females.

According to the Centers for Disease Control and Prevention (CDC), the suicide rate across the US population in 2019 was 13.9 suicide deaths per 100,000 people.[70] The CDC reported suicide as the second leading cause of death in Americans ages 15 to 34 years. However, approximately 50% of suicides occurred in Americans ages 35 to 64 years. The suicide rate was highest in adults older than 75 years, with a rate of 19 suicide deaths per 100,000 people. Among older adults, the rate was higher for men older than 75 years, with a rate of 40.5 suicide deaths per 100,000 men.

Associated Factors

MEANS

The most common means of suicide vary by age group.[65] In older adolescents and adults, firearms are the most common method, followed by suffocation (eg, hanging, strangulation) and poisoning. In children and younger adolescents, suffocation is the most common method.

SOCIOECONOMIC RISK FACTORS

A Danish study examined socioeconomic risk factors for suicide from 2014-2017.[71] Unemployment, low income, and living alone were identified as factors. Environmental factors included geographic and social isolation, low access to clinical resources, unemployment, and poverty. Protective factors included living with a partner and having a higher level of education. In general, people with higher levels of education tend to have higher incomes; thus, it may be the higher income that acts as a protective factor in the highly educated population. Others found to be at lower risk included people with a history of being a non-western immigrant or first-generation immigrant.

RACIAL AND ETHNIC ASSOCIATIONS

Recent CDC statistics indicate that American Indian/Alaska Native people have the highest risk of suicide, followed by White, then Hispanic, then Black people.[72] In 2020, suicide rates among racial and ethnic groups were

highest in non-Hispanic American Indian/Alaska Native people.[73] Suicide rates decreased for White people from 2019-2020, but increased for Black and American Indian/Alaska Native people.[70] It should be noted that race is not a biological risk factor for suicide, but rather may reflect social, cultural, familial, or other nonbiological effects, including underinvestment in mental health resources.

LGBT INDIVIDUALS

Adolescents who identify as lesbian, gay, or bisexual are four times more likely than their heterosexual peers to report a suicide attempt.[70] Studies on suicidality in transgender individuals have shown the lifetime prevalence of suicidal thoughts to be four times higher in these individuals than in those in the general population.[74] The lifetime prevalence of suicide attempts has been found to be six times higher in transgender individuals than in others.

ASSOCIATION WITH MENTAL DISORDERS

Approximately half of people who died by suicide were not known to have a current mental health diagnosis.[75] Approximately one-third were known to have depressed mood at the time of death. Patients with mental disorders, including schizophrenia, major depressive disorder (MDD), bipolar disorder, and substance use disorder, are at increased risk of suicide.[69,76] A lifetime history of depression is associated with double the likelihood of a suicide attempt.[76] Patients with bipolar I disorder have a suicide rate 15 times higher than that of individuals in the general population.[69] A high risk of suicide was identified in patients recently discharged from psychiatric hospitals.

SEASONAL VARIATIONS

Numerous epidemiologic studies have shown increased rates of suicide in the spring and early summer months. The rate of suicide completed by violent means increases in the spring and decreases in the winter, coinciding with overall patterns of suicide seasonality.[77]

This trend is thought to have a multifactorial etiology, including seasonal environmental factors (eg, increasing temperature, increased airborne allergen levels).[77] Theories for these trends include increased exacerbations in allergies and inflammatory conditions. Another suggested factor is seasonal changes in the serotonin system that increase impulsive, aggressive behaviors, including suicide attempts.[78] Increases in temperature are thought to increase the activity of brown adipose tissue, which functions to enhance cold tolerance through reduction of heat tolerance, a process that increases anxiety and psychomotor agitation.[77] It is important to note that these are observed associations and causation cannot be proven.[78]

Attempt vs Completion

In the United States, suicidal thoughts affect approximately 9% of individuals over their lifetimes.[79] The prevalence of suicide attempts is approximately 0.8%, and the prevalence of death by suicide is 0.014%.

Prediction and prevention of death by suicide are difficult among patients with suicidal thoughts. Evidence-based models have struggled to predict which patients are at highest risk.[79] Approximately one-third of patients who die by suicide have not had contact with medical or mental health services in the 30 days before their deaths, making preventive efforts difficult.

A report from the CDC National Violent Death Reporting System (NVDRS) from 2019 found risk factors specifically associated with death by suicide as opposed to risk factors for suicide attempts.[75] Death by suicide was more frequent in patients with a current mental health condition that affected their thinking, feeling, or mood and in patients ever treated for a mental health condition.

The report found that approximately one-third of people who died by suicide left a suicide note.[75] Approximately 27% of individuals who died by suicide experienced a life crisis within the preceding 2 weeks or anticipated one in the following 2 weeks. An intimate partner problem was cited in approximately 27% of cases. A history that included suicidal thoughts, intents, disclosures, and previous attempts was associated with a substantial number of suicide deaths. This information may assist in continued development of suicide prevention strategies for high-risk populations.

Screening

RECOMMENDATIONS

The 2014 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for suicide risk in adolescents, adults, and older adults concluded there is currently insufficient evidence to assess the harm vs benefit of suicide risk screening in primary care.[76] The USPSTF found insufficient evidence to conclude that such screening would identify patients at risk of suicide who would not otherwise be identified based on existing mental health conditions, emotional distress, or a history of suicide attempt.

The more recent 2022 USPSTF statement on screening for suicide risk in children and adolescents also concluded there was insufficient evidence to assess the balance of benefits and harms of screening.[80] As of the publication date of this edition, development of an updated USPSTF recommendation statement on screening for depression and suicide risk in adults was in progress.[81]

Data on screening tools for suicide risk are limited, and the tools used vary widely in accuracy.[76] Screening may be more beneficial in higher risk groups. Alternatives to

generalized screening may include focused screening and intervention for patients in high-risk circumstances, such as after a recent psychiatric hospitalization or emergency department visit for intentional self-harm.

TOOLS

Many tools have been studied to assess reliable methods of screening for suicidality and to stratify suicide risk in patients with positive screening results.[81] Most of these tools have been evaluated in settings other than primary care, such as the emergency department, inpatient hospital ward, or behavioral health specialty centers.[82]

One study of adults who presented to an emergency department for psychiatric concerns found the Columbia-Suicide Severity Rating Scale (C-SSRS) to be a suitable tool for evaluating patients for suicidal ideation and behavior in this setting.[83] The Ask Suicide-Screening Questions (ASQ) (*Table 4*) screening instrument has been shown to identify suicide risk in pediatric patients being evaluated for medical or psychiatric concerns in the emergency department.[84]

Few studies have validated or compared suicide screening tools in the primary care setting. The sensitivity and specificity of these tools have been shown to vary substantially when they are used in a primary care setting, and no tools have been evaluated in more than one study.[85] As such, there currently is minimal evidence to support widespread use of suicide risk screening tools for identification of high-risk adults in the primary care setting. When such screening tools are used, a significant number of false-positive results has been found to occur.

Management

RISK ASSESSMENT

When risk factors and protective factors have been identified, physicians can further evaluate the imminent suicide risk for an individual patient.[86,87] Physicians should ask patient-specific questions regarding suicidal thoughts, plans, behaviors, and intentions. It is important to ascertain whether a patient has had suicidal ideation and to determine the frequency and duration of such ideation.

Contrary to some assumptions, directly questioning a patient about suicide does not increase the patient's risk of completing suicide.[88] Physicians should ask patients about any suicide plans and about the details of timing, location, means, and any preparations for the act.[87] Information should be gathered about any previous suicide attempts

TABLE 4
Ask Suicide-Screening Questions

Ask the patient:

1. In the past few weeks, have you wished you were dead?	Yes or No
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?	Yes or No
3. In the past week, have you been having thoughts about killing yourself?	Yes or No
4. Have you ever tried to kill yourself?	Yes or No
If yes, how? _____	
When? _____	
If patient answers "Yes" to any of above, ask the following question:	Yes or No
5. Are you having thoughts of killing yourself right now?	
If yes, please describe: _____	

Next steps:

- If patient answers "No" to questions 1-4, screening is complete (not necessary to ask question 5). No intervention is necessary; however, note that clinical judgment can always override a negative screening result.
- If patient answers "Yes" to any of questions 1-4 or refuses to answer, this is considered a positive screening result. Ask question 5 to assess acuity.

"Yes" to question 5: acute positive screen (imminent risk identified)

Patient requires an immediate safety/full mental health evaluation. Patient cannot leave until evaluated for safety.

Keep patient in sight. Remove all dangerous objects from room. Alert physician or clinician responsible for patient's care.

"No" to question 5: nonacute positive screen (potential risk identified)

Patient requires a brief suicide safety assessment to determine if a full mental health evaluation is needed. Patient cannot leave until evaluated for safety.

Alert physician or clinician responsible for patient's care.

Resources for patients

988 Suicide & Crisis Lifeline: Call or text 988

Adapted from National Institute of Mental Health. Ask Suicide-Screening Questions. Suicide risk screening tool. https://www.nimh.nih.gov/sites/default/files/documents/research/research-conducted-at-nimh/asq-toolkit-materials/asq-tool/screening_tool_asq_nimh_toolkit.pdf

or self-injurious behaviors. Details regarding suicidal intent should be discussed, including the extent to which the patient expects to carry out the plan, how strongly the patient believes the plan will result in death, and any factors that may contribute to indecision about carrying out the plan.

A suicide risk level should be estimated for the patient.[87] *Table 5* shows factors that may assist the physician in assessing risk and provides possible routes of management. This risk level should be re-evaluated continually, particularly if any life stressors are present or change.

Physicians should document the suicide risk level and the clinical reasoning used to estimate the risk level.[87] The management plan to decrease suicide risk should be detailed, and include plans for pharmacotherapy, psychotherapy, specialist consultations, and a patient-physician shared plan for modification of the patient's environment and social interactions.[87]

PHARMACOTHERAPY

Selective serotonin reuptake inhibitors. The goal of pharmacotherapy in patients with suicidality is management of comorbid mood disorders, most often MDD. Selective serotonin reuptake inhibitors (SSRIs) are one of the most frequently prescribed classes of antidepressant drugs used to manage mood disorders.[89]

However, the Food and Drug Administration (FDA) has issued boxed warnings for SSRIs about an increased risk of suicidal thoughts and behavior in children, adolescents, and young adults taking these drugs.[90] Physicians have been cautioned to closely monitor these patients for clinical worsening of their condition. These warnings and precautions were developed primarily from randomized controlled trials with short follow-up periods that can be difficult to translate to clinical practice.[89]

An additional challenge in assessing the increased risk of suicide in patients taking SSRIs is the fact that these

TABLE 5
Suicide Risk Level Assessment and Triage

Risk Level	Risk/Protective Factor	Suicidality	Possible Interventions
High	Psychiatric diagnoses with severe symptoms or acute triggering event; protective factors irrelevant	Potentially lethal suicide attempt or persistent ideation with strong intent or rehearsal	Admission indicated unless significant change reduces risk; suicide precautions
Moderate	Multiple risk factors, few protective factors	Suicidal ideation with plan, but no intent or behavior	Admission may be needed, depending on risk factors Develop crisis plan Give emergency/crisis numbers
Low	Modifiable risk factors, strong protective factors	Thoughts of death; no plan, intent, or behavior	Outpatient referral, symptom reduction Give emergency/crisis numbers
Risk factors: Prior suicide attempt Substance or alcohol abuse Chronic disease, disability Mental disorders Access to firearms Social isolation Loss of financial status Loss of relationship		Protective factors: Social support Responsibility to children, pets Effective mental health treatment Ability to cope with stress Religious beliefs	

Adapted from Substance Abuse and Mental Health Services Administration. SAFE-T pocket card: suicide assessment five-step evaluation and triage. Dept of Health and Human Services; 2009; HHS Publication No. (SMA) 09-4432 CMHS-NSP-0193. https://store.samhsa.gov/sites/default/files/d7/priv/sma09-4432.pdf

patients already are at increased risk because of the comorbid mood disorder.[89] As such, it is important to conduct a baseline assessment of a patient's suicidal ideation before starting SSRI therapy.

Despite many studies examining the role of antidepressant initiation in activating symptoms and increased risk of suicide, the causality remains unclear.[89] Precautions that can be taken include starting SSRIs at low doses in children and adolescents; monitoring these patients closely with short-term, frequent follow-up; and titrating SSRI dosages slowly.

Esketamine and ketamine. Esketamine, the *S*-enantiomer of ketamine, is as an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor.[26,91] In 2019, the FDA approved esketamine nasal spray for management of depressive symptoms, in conjunction with an oral antidepressant, in adults with MDD and acute suicidal ideation or behavior. However, the prescribing information notes that the effectiveness of esketamine in preventing suicide or reducing suicidal ideation has not been shown.[91]

Because of the risks of sedation, dissociation, and misuse, esketamine use is regulated through a Risk Evaluation and Mitigation Strategy (REMS) program.[26,91] This requires dispensing pharmacies, prescribers, and patients receiving the drug to be enrolled in a REMS registry.[26] Patients should be informed about the serious adverse effects associated with esketamine use.

Currently, intravenous (IV) ketamine is FDA-approved for anesthesia induction and maintenance, and is used off-label to manage treatment-resistant depression in adults.[92] Studies have shown that single doses of IV ketamine can provide rapid relief of treatment-resistant depression. Longer term studies are needed to determine the efficacy and safety of IV ketamine for management of depression with suicidality.

NONPHARMACOTHERAPY

Use of "no harm contracts" or "safety contracts," in which patients attest that they will not commit suicide, should not be relied on to the exclusion of a formal suicide risk assessment and thorough clinical evaluation.[86,93] These documents have not been shown to significantly decrease suicide risk and do not provide physicians with legal protection.

One technique for suicide prevention in clinical practice is known as safety planning. These plans often involve use of cognitive behavioral therapy techniques to reduce the imminent risk of a suicide attempt in a high-risk patient.[94,95] The patient and physician develop a written list of coping strategies and sources of support to be used by the patient in times of crisis. *Figure 2* provides an example plan. Subsequent psychotherapy can help the patient further strengthen these coping mechanisms.

Safety Plan

Step 1: Warning signs:

1. Suicidal thoughts and feeling worthless and hopeless
2. Urges to drink
3. Intense arguing with girlfriend

Step 2: Internal coping strategies – Things I can do to distract myself without contacting anyone:

1. Play the guitar
2. Watch sports on television
3. Work out

Step 3: Social situations and people that can help to distract me:

1. AA Meeting
2. Joe Smith (cousin)
3. Local Coffee Shop

Step 4: People who I can ask for help:

1. Name Mother Phone 333-8666
2. Name AA Sponsor (Frank) Phone 333-7215

Step 5: Professionals or agencies I can contact during a crisis:

1. Clinician Name Dr John Jones Phone 333-7000
   Clinician Pager or Emergency Contact 555 822-9999
2. Clinician Name _____ Phone _____
   Clinician Pager or Emergency Contact # _____
3. Local Hospital ED City Hospital Center
   Local Hospital ED Address 222 Main St
   Local Hospital ED Phone 333-9000
4. Suicide Prevention Lifeline Phone: 1-800-273-TALK

Making the environment safe:

1. Keep only a small amount of pills in home
2. Don't keep alcohol in home
3. _____

Figure 2. Safety Plan Example

Reprinted from Stanley B, Brown GK. Safety planning intervention: a brief intervention to mitigate suicide risk. Cogn Behav Pract. *2012;19(2):256-264.*

For patients considering suicide, the negative effects of a suicide on family members often are a concern. Physicians can explore this concern in a positively framed manner, rather than in a guilt- or shame-inducing manner, which can make concern about family members a protective factor.[96]

There is mixed evidence to support the use of psychotherapy for patients with depression and suicidality.[97] A meta-analysis on psychotherapy for depression management found no studies that included suicide attempts or suicide deaths as outcome variables. The meta-analysis found insufficient evidence of a decrease in suicidality after psychotherapy. Other studies have shown that psychotherapy may reduce the frequency of suicidal actions through cognitive behavioral and dialectical behavior therapies.[79]

Follow-up Care

Patients who have attempted suicide have specific ongoing needs. They are at increased risk of depression, substance use, and domestic violence.[98] They are more likely to develop chronic conditions, including metabolic and systemic inflammatory conditions. Patients with a history of a suicide attempt are at increased risk of subsequent death by suicide.

Case 3, cont'd. You directly ask ZT about specific thoughts of self-harm and suicidal plans. He explains that he feels hopeless but says he has not created a specific suicide plan. You ask if he has access to any lethal means, such as weapons or high-risk drugs, and he confirms that he does not. You ask about protective factors against suicide, and ZT says he would never want to abandon his young daughter. You thoroughly review the depressive symptoms and determine they are significant. You prescribe a selective serotonin reuptake inhibitor and refer ZT to a psychologist for cognitive behavioral therapy.

SECTION FOUR

Generalized Anxiety and Panic Disorders

Anxiety disorders are characterized by excessive fear and worry. Generalized anxiety disorder (GAD) and panic disorder (PD) are two of the most common anxiety disorders in the United States. GAD is defined as excessive worry and anxiety that occur on most days for at least 6 months that affect daily functioning. PD is defined by recurrent unexpected panic attacks. Patients with symptoms of GAD or PD should be assessed for conditions such as hyperthyroidism, hyperparathyroidism, and cardiac arrhythmia before confirmation of an anxiety disorder diagnosis. A U.S. Preventive Services Task Force (USPSTF) draft statement recommends screening for anxiety in adults 64 years and younger, including pregnant and postpartum women. A final statement recommends screening for anxiety in children and adolescents ages 8 to 18 years. Multiple self-report tools have been validated for GAD and PD screening. The 7-item Generalized Anxiety Disorder (GAD-7) scale is an option for screening for GAD. The Panic Disorder Severity Scale (PDSS) is a 7-item tool with excellent sensitivity and specificity in screening for PD. Management with selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors in combination with psychotherapy has been shown to be effective for GAD and PD. Research on alternative treatments, such as psychedelic-assisted psychotherapy, is ongoing.

Case 4. JN is a 24-year-old woman who is a graduate student at a local university. She has a history of irritable bowel syndrome, which was diagnosed 3 years ago. Today she reports worsening heart palpitations and worry as she progresses through her graduate program. She says she has experienced extreme worry since adolescence. As she has grown older, the worrying has become more frequent, occurring 4 to 5 days per week. Most recently, she has noticed physical symptoms, including palpitations, dizziness, and diarrhea. She says that some days the worry keeps her from going to class or spending time with friends.

Epidemiology

Anxiety disorders are characterized by excessive fear and worry.[2] Generalized anxiety disorder (GAD) and panic disorder (PD) are two of the most common anxiety disorders in the United States.[99] GAD and PD result in increased health care use and costs.

Among US adults, the 12-month prevalence of GAD is 2.9%.[2] Around the world, the prevalence is 1.3%, with a range of 0.2% to 4.3%. The estimated 12-month prevalence of PD is 2% to 3% in adolescents and adults in the United States and several European countries. The global lifetime prevalence of PD is approximately 1.7%.

Diagnosis of GAD and PD may be delayed. Patients with these disorders may present with somatic symptoms that may require evaluation before an accurate diagnosis can be made.[99]

Management of GAD and PD often is delayed as well. A World Health Organization (WHO) survey found a delay from 3 to 30 years before patients with anxiety disorders sought treatment.[100] One study showed an average of approximately 80 months between GAD symptom onset and treatment initiation.[101] Another study found that in countries with high-quality mental health care and/or strong primary care systems, 48% to 49% of adults did not seek treatment for an anxiety or depressive disorder in the first year after symptom onset.[100] Treatment delay has been shown to negatively affect daily functioning and quality of life.[101]

Risk Factors

There is overlap in the biological and social risk factors for GAD and PD. Both disorders have a genetic component.[2,101] Patients with a family member with GAD or PD are more likely to have one of these disorders. Females are twice as likely to be diagnosed with GAD or PD as males.

Social factors include race, ethnicity, and socioeconomic status, as well as investment in community health and mental health systems. Cultural acceptability of the diagnosis and expression of mental health symptoms may play roles in symptom development and diagnosis.[2,100] There are significantly lower prevalences of GAD and PD among African, Asian, and Latinx Americans than in non-Latinx White Americans.[2] People from high-income countries are more likely than people from low- and middle-income countries to report symptoms that meet criteria for a GAD diagnosis.

Other risk factors include substance use disorder (eg, tobacco, alcohol, illicit drugs), adversities and early life stressors, and a history of traumatic events.[2,101]

Generalized Anxiety Disorder

CLINICAL DEFINITION

A sense of anxiety or worry is a common and normal phenomenon experienced by all people.[99] Nonpathologic anxiety occurs in response to typical everyday stressors. The response is adaptive and serves to improve functioning. However, the excessive anxiety and worry associated with GAD are pathologic and affect daily functioning.[2] Patients with GAD often describe their worry as so pervasive that it is disabling.[102] In GAD, the anxiety and worry are pronounced and distressing, have a long duration, and occur without precipitating factors.

The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision) (*DSM-5-TR*) defines GAD as excessive anxiety and worry about events or activities (eg, work, school) that occurs on most days for at least 6 months.[2] The worry is difficult to control. The anxiety and worry must be associated with three or more of the following symptoms, with at least some symptoms present most days for the past 6 months: restlessness or feeling on edge; being easily fatigued; difficulty concentrating; irritability; muscle tension; and sleep disturbance. Only one of these symptoms must be present in children.

The anxiety, worry, or physical symptoms must cause significant distress or impairment in functioning.[2] The symptoms must not be attributable to substance use or another condition, or be better explained by a different mental disorder.

DIAGNOSIS AND EVALUATION

Symptoms of GAD can mimic those of other conditions. In addition to excessive worry and anxiety, patients with GAD may have physical symptoms, such as trembling or twitching associated with muscle tension, sweating, nausea, diarrhea, and an exaggerated startle response.[2] Less common symptoms include accelerated heart rate, dyspnea, and dizziness. These symptoms can mimic those of conditions such as hyperthyroidism, cardiac arrhythmia, or transient ischemic attacks.[103] Thus, in patients with suspected GAD, physicians should take a thorough history, perform a physical examination, and obtain appropriate diagnostic tests to rule out other conditions.[99]

When taking the history, physicians should ask about caffeine intake and drugs such as albuterol or decongestants that could cause or exacerbate anxiety.[103,104] Diagnostic tests such as thyroid function tests, electro- or echocardiogram, or toxicology screening can be obtained.[104] Patients with GAD may have comorbidities such as substance use disorder, posttraumatic stress disorder, or bipolar disorder.[2,103] The initial evaluation should include consideration of the differential diagnoses.

SCREENING

In September 2022, the U.S. Preventive Services Task Force (USPSTF) released a draft statement recommending that adults 64 years and younger, including pregnant and postpartum women, be screened for anxiety.[105] In October 2022, it released a final statement recommending that children and adolescents ages 8 to 18 years be screened.[106] The Women's Preventive Services Initiative (WPSI), a national group of women's health organizations led by the American College of Obstetricians and Gynecologists (ACOG), recommends screening for anxiety in adolescent girls 13 years and older and in women, including pregnant and postpartum women.[107]

Multiple self-report tools exist to screen for GAD. Among these, the 7-item Generalized Anxiety Disorder (GAD-7) scale is used widely. In a systematic review that compared the GAD-7 with five other self-report tools, the GAD-7 was found to have adequate sensitivity (89%) and specificity (83%) when a cutoff score of 10 or greater was used.[99] Among the six scales reviewed, the GAD-7 was the only measure to show test-retest reliability.

The GAD-7 consists of seven questions with a score range of 0 to 21.[99] It is written at an accessible literacy level and takes approximately 2 minutes to complete. A higher GAD-7 score indicates a greater level of functional impairment.[108]

Panic Disorder

CLINICAL DEFINITION

Panic disorder is defined as panic attacks that are recurrent and unexpected and occur without a clear trigger.[2] The attacks may be frequent, occurring daily, or moderate, occurring once per week. Less frequent panic attacks may occur 1 to 2 times per month over many years.

The *DSM-5-TR* defines a panic attack as an abrupt surge of intense fear or discomfort that peaks within minutes, during which time four or more of the following symptoms occur: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of dyspnea; feelings of choking; chest pain or discomfort; nausea or abdominal distress; feelings of dizziness or light-headedness; chills or sensations of heat; paresthesias; derealization or depersonalization; fear of loss of control; and fear of dying.[2]

At least one panic attack must be followed by 1 month or longer of one or both of the following: persistent worry about additional panic attacks or their consequences and/or a significant maladaptive change in behavior related to the panic attacks.[2] All of these symptoms must not be attributable to substance use or another condition, or be better explained by a different mental disorder.

There are two types of this disorder: full-symptom PD and limited-symptom PD.[2] Full-symptom PD is characterized by four or more symptoms, and limited-symptom PD by fewer than four symptoms. However, for a diagnosis of PD, a patient must have experienced more than one unexpected, full-symptom panic attack.

A significant criterion for PD is that the patient worries about panic attacks and occurrence of symptoms.[2] They may worry that the panic attack will occur in a social setting that will lead to embarrassment, or may fear being negatively judged by others. Thus, patients with PD may avoid physical exertion and/or daily activities, such as grocery shopping or use of public transit. They may restructure their lives to prevent panic attacks.

DIAGNOSIS AND EVALUATION

Other conditions can cause symptoms similar to those of PD. These include hyperthyroidism, hyperparathyroidism, arrhythmias, supraventricular tachycardia, asthma, and chronic obstructive pulmonary disease.[2,103] Thus, obtaining appropriate laboratory tests (ie, thyroid function tests, serum calcium levels) and other diagnostic measures (eg, electrocardiogram, Holter monitor) is important.[2] Many patients with PD have comorbid mental disorders with panic attacks or specific phobias.

SCREENING

Multiple self-report tools are available to screen for PD. The Panic Disorder Severity Scale (PDSS) is a commonly used, 7-item tool that rates overall severity of PD.[109] Each item is rated on a scale from 0 to 4 points. With a cutoff score of 8 points, it has been shown to have adequate sensitivity (83%) and specificity (64%) for detecting PD. Another screening tool is the Patient Health Questionnaire-Panic Disorder (PHQ-PD). This tool has been found to have adequate sensitivity (81%) and specificity (99%) for detecting PD when there are positive responses to all five questions.[99] Both of these tools are brief and can be administered quickly in the office setting.

Management

The management approaches for GAD and PD are similar, and primarily consist of pharmacotherapy and psychotherapy.[110] In a patient with GAD, if symptoms are mild, transient, and without associated functional impairment, management is not always indicated. It is indicated if a patient shows marked distress or has significant functional impairment.

The patient and physician should engage in shared decision-making when choosing a management plan. Patient preference, history of previous treatments, severity of GAD or PD, comorbidities, and other factors (eg, cost, wait times for appointments) should be considered.[110]

PHARMACOTHERAPY

Table 6 lists drugs used for GAD and PD management.

Antidepressants. The first-line drugs for GAD and PD management are selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs).[111,112] The SSRIs inhibit serotonin reuptake, as well as weakly inhibit dopamine and norepinephrine reuptake, which is thought to increase the level of these neurotransmitters in the synapses.[111] The SNRIs also inhibit serotonin and norepinephrine reuptake in the synapses. These drugs typically are well-tolerated and have fewer adverse effects than other drugs for GAD and PD management.[112]

A meta-analysis showed that duloxetine, venlafaxine, and escitalopram were more effective than placebo for GAD management.[113] Duloxetine and escitalopram were among the best tolerated.[112] SSRIs and SNRIs can take 2 to 4 weeks to become effective, and their adverse effects are strongest during the first 2 weeks.[110] SNRIs are used widely for anxiety disorder management, but only venlafaxine has been approved by the Food and Drug Administration (FDA) for both GAD and PD management.[111] Duloxetine is approved for GAD management.

The tricyclic antidepressants such as clomipramine and imipramine are second-line drugs.[112] These are associated with multiple adverse effects, including weight gain, dry mouth, sedation, urinary hesitancy or retention, arrhythmias, and increased risk of death from overdose.[112] Because of their low tolerability, they are options for patients who do not experience symptom improvement after multiple trials of SSRIs or SNRIs.[111]

Buspirone and other drugs. Buspirone, an azapirone, is a nonbenzodiazepine anxiolytic used as a second-line treatment for GAD in adults.[111,112] Compared with placebo, buspirone has been shown to be effective for GAD management.[112] However, it has not been shown to be as effective as antidepressants. Buspirone often is used as an adjunctive drug with SSRIs or SNRIs, although research suggests there is no incremental benefit when it is added. A Cochrane review found that azapirones were more effective in patients who had never taken benzodiazepines.[114]

Buspirone typically is prescribed to be taken 2 to 3 times/day, with a gradual onset of action of approximately 10 days to 4 weeks.[112] Adverse effects include nausea, dizziness, headaches, and movement disorders.

Other drugs have been used off-label for anxiety disorder management with variable effectiveness. These include pregabalin, hydroxyzine, and quetiapine.

TABLE 6
Drugs for Generalized Anxiety and Panic Disorder Management

Drug Class	Drug	FDA Approval		Therapeutic Dosage Range (mg/day)	Adverse Effects
		GAD	PD		
SSRIs	Escitalopram	X		10-20 mg	Nausea, drowsiness, insomnia, headache, anorexia, sexual dysfunction, hyperhidrosis, diarrhea, QTc interval prolongation
	Fluoxetine		X	20-60 mg	
	Paroxetine	X	X	20-60 mg	
	Sertraline		X	50-200 mg	
SNRIs	Duloxetine	X		30-60 mg	
	Venlafaxine	X	X	75-300 mg	
TCAs	Clomipramine	Not FDA approved for GAD or PD; used off-label for both		100-250 mg	Dry mouth, drowsiness, dizziness, fatigue, tremor, headache, constipation, sexual dysfunction, weight gain
	Imipramine	Not FDA approved for GAD or PD; used off-label for both		100-300 mg	
Calcium modulator	Pregabalin	Not FDA approved for GAD or PD; used off-label for GAD		150-600 mg	Dizziness, drowsiness, peripheral edema, ataxia, weight gain, dry mouth, headache, euphoria, blurred vision, fatigue, tremor, increased appetite
Azapirone	Buspirone	X		15-60 mg	Dizziness, drowsiness, nausea, headache, excitability, insomnia

FDA = Food and Drug Administration; GAD = generalized anxiety disorder; PD = panic disorder; SNRI = selective serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Adapted from Garakani A, Murrough JW, Freire RC, et al. Pharmacotherapy of anxiety disorders: current and emerging treatment options. Front Psychiatry. *2020;11:595584; with information from Clinical Key. Clinical Pharmacology.com. https://www.clinicalkey.com/pharmacology/*

Pregabalin is a calcium modulator with sedating properties.[110] A meta-analysis showed its effectiveness and tolerability were comparable to those of escitalopram and venlafaxine for GAD management.[113] Pregabalin has an earlier onset of action than the SSRIs and SNRIs.[110] Because of its sedating properties, it should be considered for patients with sleep disorders associated with GAD.

Hydroxyzine is a sedating antihistamine that also is used off-label for anxiety disorder management.[111] Low-quality evidence supports its effectiveness. Quetiapine, an atypical antipsychotic, has mixed evidence of effectiveness. It should be noted that the dosages of quetiapine used in studies of anxiety disorders are lower than those used in studies of bipolar and psychotic disorders.

Benzodiazepines. These drugs are rapid-acting and effective in management of anxiety.[103] However, there is a dose-response relationship associated with tolerance, sedation, confusion, and increased risk of death. Overall, benzodiazepines can be used to manage anxiety symptoms in the short-term but not the long-term. Their use is associated with worse outcomes compared with use of SSRIs and SNRIs.

In GAD and PD management, benzodiazepines can be considered adjunctive drugs to another first- or second-line drug.[110,112] As noted previously, SSRIs and SNRIs can take 2 to 4 weeks to be effective. Benzodiazepines often are prescribed as adjunctive drugs to manage anxiety symptoms during this period.[110,112]

Some studies have shown that initial prescription of a benzodiazepine can lead to long-term use. One study found that 88% of patients taking benzodiazepines in a primary care setting did so on a long-term basis (ie, longer

than 180 days), although most patients also were taking an SSRI.[115]

Integrative medicine therapies. Alternative agents that have been studied for GAD management are lavender oil and kava. Lavender oil, taken orally in the form of silexan, was compared with placebo and paroxetine as a treatment for GAD.[110,111] Use of lavender oil was associated with a decrease in anxiety symptoms compared with placebo but not compared with an SSRI. Kava (*Piper methysticum*) is a root native to the Pacific Islands. Kava extract has been used for many years as an integrative medicine therapy for anxiety with some reports of effectiveness, but reports of fatal hepatotoxicity have led to bans on its use in some countries.

Psychedelic-assisted psychotherapy is an experimental approach to anxiety disorder management and represents a growing area of research. There are three chemical classes of psychedelic agents: organic tryptamines (eg, psilocybin, dimethyltryptamine [DMT]); phenethylamines (eg, mescaline); and semisynthetic ergolines (eg, lysergic acid diethylamide [LSD]). Recent studies on the safety and efficacy of these substances have found that they can improve anxiety in patients with anxiety disorders.[116]

Limited data support the use of cannabis in GAD and PD management. A case series from the United Kingdom examined patient-reported outcome measures (eg, scores from GAD-7 and other scales) at 1, 3, and 6 months after use of cannabis-based medicinal products. The study showed improvements in quality of life, but there were limits to the study design.[117] A cross-sectional study of patients using medical marijuana in Pennsylvania showed that anxiety was among the primary reasons patients reported using cannabis. Anxiety also was among the most common adverse effects reported.[118]

PSYCHOTHERAPY

Many psychotherapeutic modalities have been studied for GAD and PD management. Cognitive behavioral therapy (CBT) is effective for GAD and PD, and is considered the gold standard for GAD.[119,120] The goal of CBT is to use patient thinking and behavioral techniques to change anxiety from pathologic and intrusive to normal and tolerable.[121] Approximately 50% of patients with GAD experience improvement with CBT.[119]

Other therapies also have been studied. A meta-analysis compared cognitive therapy and relaxation therapy for GAD and PD management.[120] Both were shown to be effective for GAD, and cognitive therapy was shown to result in greater symptom reduction compared with relaxation therapy for PD.

More recently, studies have focused on metacognitive therapy (MCT). This therapy differs from CBT in that it targets specific psychological processes involved in control of thinking. The goal is elimination of negative metacognitive beliefs and creation of strategies to help patients regulate worry. One study of MCT and CBT for GAD management showed that patients who received MCT had higher recovery rates over 2 years than patients who received CBT, although both therapies were found to be effective.[119]

Referral

Family physicians commonly are the first physicians to identify, diagnose, and treat patients with GAD and PD. When initial treatment is ineffective, physicians must decide whether to change the management plan or refer the patient.

If treatment with a drug prescribed at an adequate dosage for 4 to 6 weeks does not improve symptoms, the next step is to change the drug dosage (ie, titrate to a higher dose) or change the drug.[110] When changing drugs, physicians can switch within a first-line drug class (eg, from one SSRI to another SSRI) or switch classes (eg, from an SSRI to an SNRI). The next steps are to change to second- or third-line drugs. If these treatments are ineffective, physicians should assess their comfort level with prescribing off-label drugs before considering their use. At this time, it is reasonable to refer a patient to a psychiatrist or other mental health clinician.

If a patient with GAD or PD does not benefit from education, low-intensity psychological interventions (ie, self-help, psychoeducation groups), high-intensity psychological interventions (eg, CBT, applied relaxation), or drug treatment, guidelines from the National Institute for Health and Care Excellence (NICE) recommend referral to a psychiatrist or other mental health clinician.[122]

Case 4, cont'd. You diagnose JN with generalized anxiety disorder (GAD). She meets the diagnostic criteria, as she has had excessive worry on most days for more than 6 months. Furthermore, she is not able to go to class, so the excessive worry is affecting her daily activities and impairing functioning. She reports being easily fatigued and irritable and has muscle tension, which are at least three of the six symptoms of GAD in the diagnostic criteria. You prescribe a selective serotonin reuptake inhibitor and provide a referral to a psychiatrist for psychotherapy. You advise JN to schedule a follow-up visit in 4 to 6 weeks.

References

1. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2020 National Survey on Drug Use and Health. 2021. HHS Publication No. PEP21-07-0.1-003, NSDUH Series H-56. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/reports/rpt35325/NSDUHFFRPDFWHTMLFiles2020/2020NSDUHFFR1PDFW102121.pdf
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Text revision. APA; 2022.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. APA; 2013.
4. Hudson CG. Socioeconomic status and mental illness: tests of the social causation and selection hypotheses. *Am J Orthopsychiatry*. 2005;75(1):3-18.
5. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. 2018;75(4):336-346.
6. Meader N, Mitchell AJ, Chew-Graham C, et al. Case identification of depression in patients with chronic physical health problems: a diagnostic accuracy meta-analysis of 113 studies. *Br J Gen Pract*. 2011;61(593):e808-e820.
7. Chaudhry AB, Reisner SL. Disparities by sexual orientation persist for major depressive episode and substance abuse or dependence: findings from a national probability study of adults in the United States. *LGBT Health*. 2019;6(5):261-266.
8. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry*. 2000; 157(10):1552-1562.
9. Breton JJ, Labelle R, Berthiaume C, et al. Protective factors against depression and suicidal behaviour in adolescence. *Can J Psychiatry*. 2015;60(2)(Suppl 1):S5-S15.
10. Rethorst CD, Trivedi MH. Evidence-based recommendations for the prescription of exercise for major depressive disorder. *J Psychiatr Pract*. 2013;19(3):204-212.
11. U.S. Preventive Services Task Force. Screening for depression in adults: recommendation statement. *Am Fam Physician*. 2016;94(4). https://www.aafp.org/pubs/afp/issues/2016/0815/od1.html
12. Mangione CM, Barry MJ, Nicholson WK, et al. Screening for depression and suicide risk in children and adolescents: US Preventive Services Task Force recommendation statement. *JAMA*. 2022;328(15):1534-1542.
13. Maurer DM, Raymond TJ, Davis BN. Depression: screening and diagnosis. *Am Fam Physician*. 2018;98(8):508-515.
14. Park LT, Zarate CA Jr. Depression in the primary care setting. *N Engl J Med*. 2019;380(6):559-568.
15. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA Psychiatry*. 2014;71(10): 1121-1128.
16. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. *Lancet*. 2012; 379(9820):1045-1055.
17. National Collaborating Centre for Mental Health (UK). *Depression: The Treatment and Management of Depression in Adults (Updated Edition)*. British Psychological Society; 2010.
18. Cuijpers P, Reynolds CF III, Donker T, Li J, Andersson G, Beekman A. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. *Depress Anxiety*. 2012; 29(10):855-864.
19. American Psychological Association; Guideline Development Panel for the Treatment of Depressive Disorders. Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts. https://www.apa.org/depression-guideline
20. Marcus SC, Olfson M. National trends in the treatment for depression from 1998 to 2007. *Arch Gen Psychiatry*. 2010;67(12):1265-1273.
21. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-758.
22. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018;391(10128):1357-1366.
23. American Psychiatric Association. Practice guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. APA; 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf
24. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. *J Clin Psychiatry*. 2009;70(Suppl 6):16-25.
25. Keller MB. The long-term treatment of depression. *J Clin Psychiatry*. 1999;60(Suppl 17):41-45, discussion 46-48.
26. Kritzer MD, Mischel NA, Young JR, et al. Ketamine for treatment of mood disorders and suicidality: a narrative review of recent progress. *Ann Clin Psychiatry*. 2022;34(1):33-43.
27. Hetrick SE, McKenzie JE, Bailey AP, et al. New generation antidepressants for depression in children and adolescents: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;(5):CD013674.
28. ACOG Committee on Practice Bulletins–Obstetrics. ACOG Practice Bulletin: clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol*. 2008;111(4):1001.
29. Apaydin EA, Maher AR, Shanman R, et al. A systematic review of St. John's wort for major depressive disorder. *Syst Rev*. 2016;5(1): 148.
30. Psiuk D, Nowak E, Cholewa K, Łopuszańska U, Samardakiewicz M. The potential role of serotonergic hallucinogens in depression treatment. *Life (Basel)*. 2021;11(8):765.
31. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. *N Engl J Med*. 2021;384(15): 1402-1411.
32. Andrade C, Arumugham SS, Thirthalli J. Adverse effects of electroconvulsive therapy. *Psychiatr Clin North Am*. 2016;39(3):513-530.
33. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*. 2011;68(3):241-251.

34. Bessonova L, Ogden K, Doane MJ, O'Sullivan AK, Tohen M. The economic burden of bipolar disorder in the United States: a systematic literature review. *Clinicoecon Outcomes Res*. 2020;12:481-497.

35. Tondo L, Vázquez GH, Baldessarini RJ. Prevention of suicidal behavior in bipolar disorder. *Bipolar Disord*. 2021;23(1):14-23.

36. Miller JN, Black DW. Bipolar disorder and suicide: a review. *Curr Psychiatry Rep*. 2020;22(2):6.

37. Bishop TF, Press MJ, Keyhani S, Pincus HA. Acceptance of insurance by psychiatrists and the implications for access to mental health care. *JAMA Psychiatry*. 2014;71(2):176-181.

38. Jaakkimainen L, Glazier R, Barnsley J, Salkeld E, Lu H, Tu K. Waiting to see the specialist: patient and provider characteristics of wait times from primary to specialty care. *BMC Fam Pract*. 2014;15:16.

39. Cerimele JM, Fortney JC, Pyne JM, Curran GM. Bipolar disorder in primary care: a qualitative study of clinician and patient experiences with diagnosis and treatment. *Fam Pract*. 2019;36(1):32-37.

40. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):629-640.

41. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. *Ther Adv Psychopharmacol*. 2018;8(9):251-269.

42. Marangoni C, Hernandez M, Faedda GL. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. *J Affect Disord*. 2016;193:165-174.

43. Wu MK, Wang HY, Chen YW, Lin PY, Wu CK, Tseng PT. Significantly higher prevalence rate of asthma and bipolar disorder co-morbidity: a meta-analysis and review under PRISMA guidelines. *Medicine (Baltimore)*. 2016;95(13):e3217.

44. Liang W, Chikrizhs T. Asthma history predicts the risk of affective disorders and anxiety disorders. *Health*. 2013;5(2A):313-319.

45. Tseng PT, Zeng BS, Chen YW, Wu MK, Wu CK, Lin PY. A meta-analysis and systematic review of the comorbidity between irritable bowel syndrome and bipolar disorder. *Medicine (Baltimore)*. 2016;95(33):e4617.

46. Zhao Z, Okusaga OO, Quevedo J, Soares JC, Teixeira AL. The potential association between obesity and bipolar disorder: a meta-analysis. *J Affect Disord*. 2016;202:120-123.

47. Fornaro M, Stubbs B. A meta-analysis investigating the prevalence and moderators of migraines among people with bipolar disorder. *J Affect Disord*. 2015;178:88-97.

48. Perry DC, Sturm VE, Peterson MJ, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J Neurosurg*. 2016;124(2):511-526.

49. Carta MG, Moro MF, Lorefice L, et al. The risk of bipolar disorders in multiple sclerosis. *J Affect Disord*. 2014;155:255-260.

50. Berk M, Brnabic A, Dodd S, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. *Bipolar Disord*. 2011;13(1):87-98.

51. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841-1856.

52. Family Practice Notebook. Bipolar disorder. https://fpnotebook.com/Psych/Bipolar/BplrDsrdr.htm

53. Marzani G, Price Neff A. Bipolar disorders: evaluation and treatment. *Am Fam Physician*. 2021;103(4):227-239.

54. Rhee TG, Olfson M, Nierenberg AA, Wilkinson ST. 20-year trends in the pharmacological treatment of bipolar disorder by psychiatrists in outpatient care settings. *Am J Psychiatry*. 2020;177(8):706-715.

55. Vieta E, Günther O, Locklear J, et al. Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol*. 2011;14(8):1029-1049.

56. Cheniaux E, Nardi AE. Evaluating the efficacy and safety of antidepressants in patients with bipolar disorder. *Expert Opin Drug Saf*. 2019;18(10):893-913.

57. Rhee TG, Olfson M, Wilkinson ST. Changes in pharmacotherapeutic approaches in the treatment of bipolar disorder by primary care physicians. *Gen Hosp Psychiatry*. 2020;67:141-143.

58. Miklowitz DJ, Efthimiou O, Furukawa TA, et al. Adjunctive psychotherapy for bipolar disorder: a systematic review and component network meta-analysis. *JAMA Psychiatry*. 2021;78(2):141-150.

59. Bauer IE, Gálvez JF, Hamilton JE, et al. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. *J Psychiatr Res*. 2016;74:1-7.

60. Takeshima M, Utsumi T, Aoki Y, et al. Efficacy and safety of bright light therapy for manic and depressive symptoms in patients with bipolar disorder: a systematic review and meta-analysis. *Psychiatry Clin Neurosci*. 2020;74(4):247-256.

61. Kishi T, Sakuma K, Okuya M, Ikeda M, Iwata N. Omega-3 fatty acids for treating residual depressive symptoms in adult patients with bipolar disorder: a systematic review and meta-analysis of double-blind randomized, placebo-controlled trials. *Bipolar Disord*. 2021;23(7):730-731.

62. Wilkowska A, Szałach Ł, Cubała WJ. Ketamine in bipolar disorder: a review. *Neuropsychiatr Dis Treat*. 2020;16:2707-2717.

63. Kishi T, Ikuta T, Matsuda Y, et al. Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials. *Mol Psychiatry*. 2021;26(8):4146-4157.

64. Proudfoot J, Doran J, Manicavasagar V, Parker G. The precipitants of manic/hypomanic episodes in the context of bipolar disorder: a review. *J Affect Disord*. 2011;133(3):381-387.

65. Centers for Disease Control and Prevention, Web-based Injury Statistics Query and Reporting System (WISQARS). Injury prevention & control. Leading causes of death and injury. https://www.cdc.gov/injury/wisqars/LeadingCauses.html

66. Centers for Disease Control and Prevention. Suicide rising across the US. *CDC Vital Signs*. June 2018. https://www.cdc.gov/vitalsigns/pdf/vs-0618-suicide-H.pdf

67. American Foundation for Suicide Prevention. Suicide statistics. https://afsp.org/suicide-statistics/

68. Stone DM, Jones CM, Mack KA. Changes in suicide rates – United States, 2018-2019. *MMWR Morb Mortal Wkly Rep*. 2021;70(8):261-268.

69. Baldessarini RJ. Epidemiology of suicide: recent developments. *Epidemiol Psychiatr Sci*. 2019;29:e71.

70. Centers for Disease Control and Prevention. Suicide prevention: disparities in suicide. https://www.cdc.gov/suicide/facts/disparities-in-suicide.html

71. Berkelmans G, van der Mei R, Bhulai S, Gilissen R. Identifying socio-demographic risk factors for suicide using data on an individual level. *BMC Public Health*. 2021;21(1):1702.

72. Centers for Disease Control and Prevention. Suicide among adults aged 35-64 years—United States, 1999-2010. *MMWR Morb Mortal Wkly Rep*. 2013;62(17):321-325.

73. Ehlman DC, Yard E, Stone DM, Jones CM, Mack KA. Changes in Suicide Rates – United States, 2019 and 2020. *MMWR Morb Mortal Wkly Rep*. 2022;71(8):306-312.

74. Herman JL, Brown T, Haas AP. *S*uicide thoughts and attempts among transgender adults: findings from the 2015 U.S. transgender survey*.* The Williams Institute at UCLA School of Law; 2019. https://williamsinstitute.law.ucla.edu/wp-content/uploads/Suicidality-Transgender-Sep-2019.pdf

75. Wilson RF, Liu G, Lyons BH, et al. Surveillance for violent deaths – National Violent Death Reporting System, 42 states, the District of Columbia, and Puerto Rico, 2019. *MMWR Surveill Summ*. 2022; 71(6):1-40.

76. LeFevre ML. Screening for suicide risk in adolescents, adults, and older adults in primary care: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(10):719-726.

77. Woo JM, Okusaga O, Postolache TT. Seasonality of suicidal behavior. *Int J Environ Res Public Health*. 2012;9(2):531-547.

78. Akkaya-Kalayci T, Vyssoki B, Winkler D, et al. The effect of seasonal changes and climatic factors on suicide attempts of young people. *BMC Psychiatry*. 2017;17(1):365. 10.1186/s12888-017-1532.

79. Paris J. Can we predict or prevent suicide? An update. *Prev Med*. 2021;152(Pt 1):106353.

80. U.S. Preventive Services Task Force. Final recommendation statement. Depression and suicide risk in children and adolescents: screening. https://uspreventiveservicestaskforce.org/uspstf/recommendation/screening-depression-suicide-risk-children-adolescents

81. U.S. Preventive Services Task Force. Draft recommendation statement. Depression and suicide risk in adults: screening. https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/screening-depression-suicide-risk-adults

82. Screening for suicide risk: recommendation and rationale. *Am Fam Physician*. 2004;70(11):2187-2190.

83. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277.

84. Horowitz LM, Bridge JA, Teach SJ, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. *Arch Pediatr Adolesc Med*. 2012;166(12):1170-1176.

85. Screening for suicide risk in adolescents, adults, and older adults in primary care: recommendation statement. *Am Fam Physician*. 2015;91(3):190F-I.

86. Jacobs DG, Baldessarini RJ, Conwell Y, et al; American Psychological Association. Practice guideline for the assessment and treatment of patients with suicidal behaviors. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/suicide-1410197760903.pdf

87. Substance Abuse and Mental Health Services Administration. Suicide SAFE-T pocket card: suicide assessment five-step evaluation and triage. Dept of Health and Human Services; 2009. HHS Publication No. (SMA) 09-4432 CMHS-NSP-0193.

88. Dazzi T, Gribble R, Wessely S, Fear NT. Does asking about suicide and related behaviours induce suicidal ideation? What is the evidence? *Psychol Med*. 2014;44(16):3361-3363.

89. Lagerberg T, Fazel S, Sjölander A, Hellner C, Lichtenstein P, Chang Z. Selective serotonin reuptake inhibitors and suicidal behaviour: a population-based cohort study. *Neuropsychopharmacology*. 2022; 47(4):817-823.

90. Friedman RA. Antidepressants' black-box warning—10 years later. *N Engl J Med*. 2014;371(18):1666-1668.

91. Spravato (esketamine). Package insert. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf

92. Parikh SV, Lopez D, Vande Voort JL, et al. Developing an IV ketamine clinic for treatment-resistant depression: a primer. *Psychopharmacol Bull*. 2021;51(3):109-124.

93. Simon RI. The suicide prevention contract: clinical, legal, and risk management issues. *J Am Acad Psychiatry Law*. 1999;27(3): 445-450.

94. Nuij C, van Ballegooijen W, de Beurs D, et al. Safety planning-type interventions for suicide prevention: meta-analysis. *Br J Psychiatry*. 2021;219(2):419-426.

95. Stanley B, Brown GK. Safety planning intervention: a brief intervention to mitigate suicide risk. *Cognit Behav Pract*. 2012;19(2): 256-264.

96. Ford J, Thomas F, Byng R, McCabe R. Asking about self-harm and suicide in primary care: moral and practical dimensions. *Patient Educ Couns*. 2021;104(4):826-835.

97. Cuijpers P, de Beurs DP, van Spijker BA, Berking M, Andersson G, Kerkhof AJ. The effects of psychotherapy for adult depression on suicidality and hopelessness: a systematic review and meta-analysis. *J Affect Disord*. 2013;144(3):183-190.

98. Tong B, Kashdan TB, Joiner T, Rottenberg J. Future well-being among people who attempt suicide and survive: research recommendations. *Behav Ther*. 2021;52(5):1213-1225.

99. Herr NR, Williams JW Jr, Benjamin S, McDuffie J. Does this patient have generalized anxiety or panic disorder? The Rational Clinical Examination systematic review. *JAMA*. 2014;312(1):78-84.

100. Waumans RC, Muntingh ADT, Draisma S, Huijbregts KM, van Balkom AJLM, Batelaan NM. Barriers and facilitators for treatment-seeking in adults with a depressive or anxiety disorder in a Western-European health care setting: a qualitative study. *BMC Psychiatry*. 2022;22(1):165.

101. Dell'Osso B, Camuri G, Benatti B, Buoli M, Altamura AC. Differences in latency to first pharmacological treatment (duration of untreated illness) in anxiety disorders: a study on patients with panic disorder, generalized anxiety disorder and obsessive-compulsive disorder. *Early Interv Psychiatry*. 2013;7(4):374-380.

102. Hirsch CR, Beale S, Grey N, Liness S. Approaching cognitive behavior therapy for generalized anxiety disorder from a cognitive process perspective. *Front Psychiatry*. 2019;10:796.

103. Locke AB, Kirst N, Shultz CG. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. *Am Fam Physician*. 2015;91(9):617-624.

104. Munir S, Takov V. *Generalized Anxiety Disorder*. In: StatPearls [Internet]. StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK441870/

105. U.S. Preventive Services Task Force. Draft recommendation statement. Anxiety in adults: screening. https://uspreventiveservicestaskforce.org/uspstf/draft-recommendation/anxiety-adults-screening

106. U.S. Preventive Services Task Force. Final recommendation statement. Anxiety in children and adolescents: screening. https://uspreventiveservicestaskforce.org/uspstf/recommendation/screening-anxiety-children-adolescents

107. Gregory KD, Chelmow D, Nelson HD, et al. Screening for anxiety in adolescent and adult women: a recommendation from the Women's Preventive Services Initiative. *Ann Intern Med*. 2020;173(1):48-56.

108. Löwe B, Decker O, Müller S, et al. Validation and standardization of the Generalized Anxiety Disorder screener (GAD-7) in the general population. *Med Care*. 2008;46(3):266-274.

109. Shear MK, Rucci P, Williams J, et al. Reliability and validity of the Panic Disorder Severity Scale: replication and extension. *J Psychiatr Res*. 2001;35(5):293-296.

110. Bandelow B, Michaelis S, Wedekind D. Treatment of anxiety disorders. *Dialogues Clin Neurosci*. 2017;19(2):93-107.

111. Strawn JR, Geracioti L, Rajdev N, Clemenza K, Levine A. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. *Expert Opin Pharmacother*. 2018;19(10):1057-1070.

112. Garakani A, Murrough JW, Freire RC, et al. Pharmacotherapy of anxiety disorders: current and emerging treatment options. *Front Psychiatry*. 2020;11:595584.

113. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. *Lancet*. 2019;393(10173):768-777.

114. Chessick CA, Allen MH, Thase M, et al. Azapirones for generalized anxiety disorder. *Cochrane Database Syst Rev*. 2006;(3):CD006115.

115. Tanguay Bernard MM, Luc M, Carrier JD, et al. Patterns of benzodiazepines use in primary care adults with anxiety disorders. *Heliyon*. 2018;4(7):e00688.

116. Weston NM, Gibbs D, Bird CIV, et al. Historic psychedelic drug trials and the treatment of anxiety disorders. *Depress Anxiety*. 2020;37(12):1261-1279.

117. Ergisi M, Erridge S, Harris M, et al. UK Medical Cannabis Registry: an analysis of clinical outcomes of medicinal cannabis therapy for generalized anxiety disorder. *Expert Rev Clin Pharmacol*. 2022;15(4):487-495.

118. Kimless D, Caloura M, Markos V, Ryan J, Abbonizio S, Janicki S. An observational cross-sectional survey exploring the indications for and responses to medical marijuana use in certified patients in Pennsylvania. *J Prim Care Community Health*. 2022;13:21501319221129734.

119. Nordahl HM, Borkovec TD, Hagen R, et al. Metacognitive therapy versus cognitive-behavioural therapy in adults with generalised anxiety disorder. *BJPsych Open*. 2018;4(5):393-400.

120. Siev J, Chambless DL. Specificity of treatment effects: cognitive therapy and relaxation for generalized anxiety and panic disorders. *J Consult Clin Psychol*. 2007;75(4):513-522.

121. Borza L. Cognitive-behavioral therapy for generalized anxiety. *Dialogues Clin Neurosci*. 2017;19(2):203-208.

122. Generalised anxiety disorder and panic disorder in adults: management. *NICE Clinical Guidelines, No. 113.* London: National Institute for Health and Care Excellence; 2019. https://www.ncbi.nlm.nih.gov/books/NBK552847/

Additional Resources

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text revision. APA; 2022.

American Psychological Association. Clinical practice guideline for the treatment of depression across three age cohorts. https: //www.apa.org/depression-guideline

Borza L. Cognitive-behavioral therapy for generalized anxiety. *Dialogues Clin Neurosci.* 2017;19(2):203-208.

Gliatto MF, Rai AK. Evaluation and treatment of patients with suicidal ideation. *Am Fam Physician.* 1999;59(6):1500-1506.

Locke AB, Kirst N, Shultz CG. Diagnosis and management of generalized anxiety disorder and panic disorder in adults. *Am Fam Physician.* 2015;91(9):617-624.

McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet.* 2020;396(10265):1841-1856.

Screening for suicide risk in adolescents, adults, and older adults in primary care: recommendation statement. *Am Fam Physician.* 2015;91(3):190F-I.

Posttest Questions

FP Essentials subscribers may complete the posttest at https://www.aafp.org/pubs/fpe/quiz.html to earn 5 AAFP Prescribed CME credits. Credit may be claimed for 2 years from the date of this edition. Each question has only one correct answer. An explanation for each correct answer is provided at the end.

1. In the United States, which one of the following age groups has the highest prevalence of at least one major depressive episode?

- ☐ A. 12 to 17 years.
- ☐ B. 18 to 25 years.
- ☐ C. 26 to 34 years.
- ☐ D. 35 to 44 years.
- ☐ E. 45 to 60 years.

2. According to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision), which one of the following symptoms of major depressive disorder is considered diagnostic in children and adolescents but not in adults?

- ☐ A. Loss of interest or pleasure in usual activities.
- ☐ B. Weight loss or gain.
- ☐ C. Insomnia.
- ☐ D. Irritable mood.
- ☐ E. Poor concentration.

3. The U.S. Preventive Services Task Force (USPSTF) recommends screening for major depressive disorder in patients 8 years and older.

- ☐ A. True.
- ☐ B. False.

4. Which one of the following is true of major depressive disorder management?

- ☐ A. Escitalopram has been shown to be the most effective drug.
- ☐ B. Sertraline is the first-line drug for adolescents.
- ☐ C. Bupropion may not be tolerated in patients with coexisting anxiety.
- ☐ D. Bright light therapy is considered a first-line nonpharmacotherapy option.

5. When is major depressive disorder considered treatment-resistant?

- ☐ A. After treatment with a selective serotonin reuptake inhibitor (SSRI) without clinical improvement.
- ☐ B. After treatment with a selective serotonin-norepinephrine reuptake inhibitor without clinical improvement.
- ☐ C. After concurrent treatment with an SSRI and at least two augmentation therapies without clinical improvement.
- ☐ D. After treatment with two antidepressants without clinical improvement.

6. According to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision), which one of the following differentiates bipolar I from bipolar II disorder?

- ☐ A. Presence of at least one suicidal episode in the patient's lifetime.
- ☐ B. Presence of at least one manic episode in the patient's lifetime.
- ☐ C. Absence of a hypomanic episode.
- ☐ D. Absence of a depressive episode.

7. Genetics are a risk factor for bipolar disorder.

- ☐ A. True.
- ☐ B. False.

8. Which one of the following is an appropriate screening test for bipolar disorder?

- ☐ A. Patient Health Questionnaire-9 (PHQ-9).
- ☐ B. World Health Organization-5 (WHO-5) Well-Being Index.
- ☐ C. Mood Disorder Questionnaire (MDQ).
- ☐ D. Geriatric Depression Scale (GDS).

9. Which one of the following is considered the gold-standard mood-stabilizing drug for bipolar disorder management?

- ☐ A. Lithium.
- ☐ B. Venlafaxine.
- ☐ C. Quetiapine.
- ☐ D. Valproic acid.
- ☐ E. Trazodone.

10. Which one of the following is true of nonpharmacotherapy options for bipolar disorder management?

- ☐ A. Psychotherapy as an adjunct to pharmacotherapy has been shown to decrease hospitalization and recurrence rates.
- ☐ B. Psychoeducation delivered in group formats has not been shown to be beneficial.
- ☐ C. Light therapy has been shown to be effective in reducing depressive symptoms.
- ☐ D. Omega-3 fatty acid supplementation as an adjunct to pharmacotherapy is supported by moderate-quality evidence.

11. Which one of the following statements is accurate about suicide epidemiology in the United States?

- ☐ A. Females are more likely to die by suicide than males.
- ☐ B. Females are more likely to attempt suicide than males.
- ☐ C. Adolescents and adults ages 15 to 34 years have the highest rate of suicide deaths.
- ☐ D. Older women are more likely to die by suicide than older men.

12. Suicide rates increase in the spring and early summer months.

- ☐ A. True.
- ☐ B. False.

13. Which one of the following summarizes the evidence behind the current U.S. Preventive Services Task Force (USPSTF) recommendation on screening for suicide risk in adolescents, adults, and older adults?

- ☐ A. Good-quality evidence supports a benefit of screening.
- ☐ B. Moderate-quality evidence supports a benefit of screening.
- ☐ C. Moderate- or high-quality evidence supports no net benefit of screening.
- ☐ D. Insufficient evidence to assess the harm vs benefit.

14. Asking a patient directly about suicidal ideation, frequency of suicidal thoughts, and suicidal plans or behaviors can increase the patient's risk of completing suicide.

- ☐ A. True.
- ☐ B. False.

15. Esketamine is approved for management of depressive symptoms, in conjunction with an oral antidepressant, in adults with major depressive disorder and acute suicidal ideation or behavior. It has been shown to be effective in preventing suicide and reducing suicidal ideation.

- ☐ A. True.
- ☐ B. False.

16. According to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision), which one of the following defines generalized anxiety disorder?

- ☐ A. Worry in response to typical everyday stressors.
- ☐ B. Excessive anxiety and worry occurring on most days for at least 2 weeks.
- ☐ C. Excessive anxiety and worry occurring on most days for at least 3 months.
- ☐ D. Excessive anxiety and worry occurring on most days for at least 6 months.

17. The U.S. Preventive Services Task Force (USPSTF) recommends screening for anxiety in adults 64 years and younger, including pregnant and postpartum women, and in children and adolescents ages 8 to 18 years.

- ☐ A. True.
- ☐ B. False.

18. Which one of the following drugs has been shown to be effective and among the best tolerated for generalized anxiety disorder management?

- ☐ A. Venlafaxine.
- ☐ B. Escitalopram.
- ☐ C. Clomipramine.
- ☐ D. Buspirone.

19. Which one of the following is true of buspirone, an azapirone, for generalized anxiety disorder management in adults?

- ☐ A. It is a first-line therapy option.
- ☐ B. It is as effective as antidepressants.
- ☐ C. It is more effective in patients who have never taken benzodiazepines.
- ☐ D. It offers incremental benefit when added to a selective serotonin reuptake inhibitor or selective serotonin-norepinephrine reuptake inhibitor.

20. Which one of the following is true of drugs used to manage anxiety disorders?

- ☐ A. Quetiapine doses used in studies of anxiety disorders are lower than those used in studies of bipolar and psychotic disorders.
- ☐ B. Hydroxyzine has high-quality evidence supporting its effectiveness.
- ☐ C. Benzodiazepines are effective second-line drugs.
- ☐ D. Pregabalin has a slower onset of action than the selective serotonin reuptake inhibitors.

Posttest Answers

Question 1: The correct answer is B.
The 2020 National Survey on Drug Use and Health (NSDUH) found that 8.4% of US adults had at least one major depressive episode. The age group with the highest prevalence (17%) was adults ages 18 to 25 years. See page 7.

Question 2: The correct answer is D.
The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision) defines major depressive disorder as five or more of the following symptoms present during a 2-week period, during which at least one of the symptoms is depressed mood or loss of interest or pleasure: depressed mood (in children and adolescents this can be irritable mood); diminished interest or pleasure in activities; significant weight loss or gain, or decreased or increased appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; poor concentration or indecisiveness; and recurrent thoughts of death or suicidal ideation, plan, or attempt. See pages 7-8.

Question 3: The correct answer is B.
The U.S. Preventive Services Task Force (USPSTF) recommends screening for major depressive disorder (MDD) in adolescents ages 12 to 18 years. However, it found insufficient evidence to assess the benefits vs harms of screening for MDD in children 11 years and younger. See page 8.

Question 4: The correct answer is C.
Bupropion may not be tolerated in patients with coexisting anxiety, and it is not effective for management of generalized anxiety. See page 11.

Question 5: The correct answer is D.
After an adequate trial of two antidepressants without clinical improvement, major depressive disorder is considered treatment-resistant. See page 11.

Question 6: The correct answer is B.
Per the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision), bipolar I disorder consists of recurring manic, depressive, and hypomanic episodes, with at least one manic episode required for the diagnosis. For a diagnosis of bipolar II disorder, a current or past hypomanic episode and a current or past major depressive episode are required. Additionally, a manic episode must never have occurred. See pages 13-14.

Question 7: The correct answer is A.
Research consistently has shown genetics to be a factor in bipolar disorder (BD), with twin studies finding a monozygotic concordance ranging from 40% to 70%. Patients with a first-degree relative with BD have a 5% to 10% lifetime of developing the disorder. See page 14.

Question 8: The correct answer is C.
One of the most frequently used screening tools for bipolar disorder (BD) is the Mood Disorder Questionnaire (MDQ), which has a sensitivity of 80% and specificity of 70% for BD. See page 14.

Question 9: The correct answer is A.
High-quality evidence supports the use of lithium as the gold-standard mood-stabilizing drug in patients with bipolar disorder (BD) and for BD maintenance therapy. It has been shown to reduce suicidality and manage manic and depressive episodes. See pages 16-18.

Question 10: The correct answer is A.
For bipolar disorder, psychotherapy as an adjunct to pharmacotherapy has been shown to decrease hospitalization and recurrence rates, improve functioning, and reduce the need for drugs. See page 18.

Question 11: The correct answer is B.
The 2018 National Survey on Drug Use and Health (NSDUH) found that females attempted suicide 1.5 times more frequently than males. See page 19.

Question 12: The correct answer is A.
Numerous epidemiologic studies have shown increased rates of suicide in the spring and early summer months. See page 20.

Question 13: The correct answer is D.
The 2014 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for suicide risk in adolescents, adults, and older adults concluded there is currently insufficient evidence to assess the harm vs benefit of suicide risk screening in primary care. See page 20.

Question 14: The correct answer is B.
Physicians should ask patient-specific questions regarding suicidal thoughts, plans, behaviors, and intentions. It is important to ascertain whether a patient has had suicidal ideation and to determine the frequency and duration of such ideation. Contrary to some assumptions, directly questioning a patient about suicide does not increase the patient's risk of completing suicide. See page 21.

Question 15: The correct answer is B.
In 2019, the Food and Drug Administration (FDA) approved esketamine nasal spray for management of depressive symptoms, in conjunction with an oral antidepressant, in adults with major depressive disorder and acute suicidal ideation or behavior. However, the prescribing information notes that the effectiveness of esketamine in preventing suicide or reducing suicidal ideation has not been shown. See page 23.

Question 16: The correct answer is D.
The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition, Text Revision) defines generalized anxiety disorder as excessive anxiety and worry about events or activities (eg, work, school) that occurs on most days for at least 6 months. See page 26.

Question 17: The correct answer is A.
In September 2022, the U.S. Preventive Services Task Force (USPSTF) released a draft statement recommending that adults 64 years and younger, including pregnant and postpartum women, be screened for anxiety. In October 2022, it released a final statement recommending that children and adolescents ages 8 to 18 years be screened. See page 26.

Question 18: The correct answer is B.
A meta-analysis showed that duloxetine, venlafaxine, and escitalopram were more effective than placebo for generalized anxiety disorder management. Duloxetine and escitalopram were among the best tolerated. See page 27.

Question 19: The correct answer is C.
Buspirone, an azapirone, is a nonbenzodiazepine anxiolytic used as a second-line treatment for generalized anxiety disorder in adults. A Cochrane review found that azapirones were more effective in patients who had never taken benzodiazepines. See page 27.

Question 20: The correct answer is A.
Quetiapine, an atypical antipsychotic, has mixed evidence of effectiveness for anxiety disorders. It should be noted that the dosages of quetiapine used in studies of anxiety disorders are lower than those used in studies of bipolar and psychotic disorders. See page 28.

Notes

Notes

The next edition of AAFP FP Essentials™ *will be:*

Respiratory Symptom Evaluation in Adults


AAFP
AMERICAN ACADEMY OF FAMILY PHYSICIANS