Depression and Suicide

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty
Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners
John M. Leonard, MD
Margaret Donohue, PhD
Alice Yick Flanagan, PhD, MSW
Margo A. Halm, RN, PhD, ACNS-BC, FAAN

Senior Director of Development and Academic Affairs
Sarah Campbell

Division Planners/Director Disclosure
The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for physicians, nurses, physician assistants, social workers, therapists, and counselors in the primary care setting who may identify and treat patients who are depressed and/or suicidal.

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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AACN Synergy CERP Category A.

Social workers completing this intermediate-to-advanced course receive 15 Clinical continuing education credits.

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NetCE designates this continuing education activity for 15 continuing education hours for addiction professionals.

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The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Course Objective
Although contact with the primary care setting represents a potential opportunity for timely identification and intervention, abundant evidence indicates that many patients with depression are inadequately diagnosed and treated in these settings. The purpose of this course is to provide the information and encouragement necessary to allow primary care providers to properly diagnose, treat, and follow-up with patients with depression.

Learning Objectives
Upon completion of this course, you should be able to:

1. Outline the epidemiology of depression and suicide.
2. Identify populations at increased risk for depression.
3. Describe the natural history and pathophysiology of depression.
4. Evaluate the signs and symptoms of depression utilizing appropriate screening tools.
5. Employ the appropriate diagnostic criteria for depression, including modifier subtypes.
6. Assess patients for depressive signs and symptoms, with particular attention to unique features in special populations.
7. Identify other conditions that can mimic or co-occur with depression.
8. Create a treatment plan for patients diagnosed with depression.
9. Compare pharmacotherapies and psychosocial therapies used in the treatment of depression.
10. Assess patients' reactions to depression treatments and identify treatment-resistance depres-sion.
11. Recognize and appropriately treat perinatal depression.
12. Review the epidemiology of suicide.
13. Describe the impact of suicide in the treatment of special populations, including among the elderly.
14. Identify risk and protective factors for suicide.
15. Evaluate tools available for the assessment and evaluation of suicide risk.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Depression is a common, debilitating mood disorder that is highly prevalent in medically ill populations, but many persons with depression are unaware they need, or are reluctant to seek, professional help. Primary care contact represents a potential opportunity for timely identification and intervention, but many patients with depression are inadequately diagnosed by non-psychiatrist clinicians, even after additional training [1; 2]. Even with accurate diagnosis, treatment is often inconsistent with current evidence, reflecting poor provider competence and confidence related to diagnosing and treating depression [3]. Adverse outcomes may result from treatment non-adherence, which can be positively influenced by patient preference for the prescribed modality and shared decision-making between physician and patient [4; 5]. Shortcomings in the delivery of care by primary care physicians, nurses, and behavioral health professionals represent an opportunity to alleviate patient distress and improve functioning through education.

For some patients with major depressive disorder (MDD), their initial antidepressant is ineffective or intolerable, and others remain impaired despite substantial symptom reduction. Inadequate patient outcomes may result from limitations in the foundation of clinical care for depression: MDD is a highly heterogeneous disorder but is diagnosed as a unitary syndrome, and almost all U.S. Food and Drug Administration (FDA)-approved medications for depression are based on a 60-year-old mechanistic

hypothesis. Knowledge advances are transforming the understanding and treatment of MDD. This course will discuss optimal use of standard diagnostic and therapeutic approaches, knowledge advances, and their consideration and integration into best practices of clinical care for patients with depression.

EPIDEMIOLOGY

INCIDENCE AND PREVALENCE OF DEPRESSION

In 2020, 18.4% of U.S. adults (one in five) reported having ever been diagnosed with depression. The prevalence of depression was higher in women, younger adults, and adults with lower education levels. Estimates of an ever diagnosis of depression ranged from 12.7% in Hawaii to 27.5% in West Virginia. Age-standardized county-level prevalence estimates ranged from 10.7% to 31.9%, with considerable state- and county-level variability [6]. Reports that focused on measures of current depression (i.e., during the prior two weeks) rather than on lifetime depression showed similar subgroup differences, including those observed both before and throughout the SARS-CoV-2 2019 (COVID-19) pandemic. Reporting from 2020 forward suggests that the COVID-19 pandemic contributed to a worsening mental health crisis in the United States, especially among adolescents and young adults [7; 8; 9]. Depression is more common in persons with medical illnesses, with 11% to 36% of general medical inpatients fulfilling diagnostic criteria for MDD [10; 11; 12; 13]. Depression also is two to three times more likely in individuals with chronic diseases, including diabetes, arthritis, and cardiovascular diseases [14].

According to data from the National Survey on Drug Use and Health (NSDUH), in 2024, an estimated 21.4 million Americans (8.2%) 18 years of age and older experienced a past-year major depressive episode, and 3.8 million (15.4%) American youth 12 to 17 years of age experienced a past-year major depressive episode [15].

DEMOGRAPHIC CHARACTERISTICS

NSDUH data indicate that women have higher rates of major depression than men in every age group (9.8% in women; 6.4% in men), with the highest rates occurring in individuals 18 to 25 years of age [15]. Rates of major depressive episodes among individuals of two or more races were 15.5%, compared with 9.1% among non-Hispanic White, 8.4% among American Indian/Alaska Native, 6.8% among Hispanic or Latino, 6.1% among Black or African American, 5.6% among Asian, and 2.1% among Native Hawaiian and Pacific Islander individuals [15]. Of the 21.4 million Americans 18 years of age and older who reported a past-year major depressive episode, approximately 15.3 million had episodes that included severe impairment. Of the 3.8 million young people 12 to 17 years of age who reported a past-year major depressive episode, approximately 2.8 million had episodes that included severe impairment. Female youth reported higher rates of severe impairment (17.2%) than male youths (5.7%) [15]. Social determinants of health (e.g., economic status, access to health care) also influence rates of depression [6]. Persons living below the poverty level are five times more likely to have current depression than those living at or above the poverty line [16].

Older Adults

The rate of depression in adults older than 65 years of age is approximately 4% in the community but increases to 13.5% in those who require home healthcare and to 11.5% in the hospitalized elderly [17]. The recurrence rate of MDD in the elderly is also extremely high, at 40% [18]. Chronic health conditions contribute to an increased risk of depression in the elderly [17].

Peripartum Women

The peripartum period may be the most common time in a woman's life for depression to develop. Between 14% and 23% of women will experience a depressive disorder while pregnant, and 10% to 15% of women will experience a depressive disorder postpartum [19; 20; 21].

Persistent Depressive Disorder

Persistent depressive disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR) represents a consolidation of DSM-IV-defined chronic MDD and dysthymic disorder. The 12-month prevalence in the United States is approximately 0.5% for persistent depressive disorder and 1.5% for chronic MDD [10]. The median age of onset of persistent depressive disorder is 31 years [22].

PERSONAL AND SOCIETAL COSTS OF DEPRESSION

Major depressive disorder exacts an enormous toll on afflicted persons and is recurrent or chronic in approximately 35% of patients. It is associated with numerous chronic medical comorbidities and complications from acute medical illness, such as myocardial infarction [22]. Interpersonal connections and role functioning as spouse, parent, or worker are impaired. MDD is the leading cause of disability in the United States for persons 15 to 44 years of age and is second only to chronic back and neck pain in disability days per year among all Americans [22].

MDD is among the most costly illnesses in the world. The cost of depression in the United States was estimated at $210.5 billion in 2010, a 21.5% increase from 2005 [23]. Approximately 50% of this figure was attributed to workplace costs, 45% to direct costs, and 5% to suicide-related costs [23; 24]. The economic burden of MDD was an estimated $334 billion in 2019, an increase of more than 41% since 2010 [25]. The direct cost of treating depression accounted for only 38% of the overall economic burden, or $127.3 billion [25]. In 2019, indirect costs were estimated at $206.4 billion, which included $126.3 billion in workplace costs (i.e., unemployment, productivity loss, absenteeism, presenteeism, and disability). Even low-grade depression is associated with decreased work productivity [26]. Patients who do not achieve full treatment response use twice as many healthcare services, and cost employers almost four times as much as patients achieving remission [27]. Women with early-onset depression (before 22 years of age) often fail to graduate from college and earn substantially less income than women with later-onset depression or no depression [28]. In the United States, the annual cost of suicidal behaviors (attempts and deaths) was estimated to be $93.5 billion in 2016 [29]. Depression causes an estimated 200 million lost workdays each year at a cost to employers of $17 to $44 billion [30]. However, attempts to quantify such costs on a national scale are hampered by incomplete data, such as the under-reporting of suicides [31].

BACKGROUND

RISK FACTORS

Several demographic/socioeconomic, psychosocial, familial, medical, and psychologic factors are associated with higher risk for depression. Adverse early life events such as early childhood parental abandonment or death, or emotional trauma from physical, sexual or emotional abuse are major risk factors for depression and other psychiatric disorders in adulthood. In adulthood, recent loss (e.g., death, divorce), domestic abuse/violence, traumatic civilian (assault, serious car accident) or military (battlefield injury, witnessing death and dismemberment) events, and major life changes (e.g., job change, financial hardships) are all potential red flags for depression [21; 32].

Women have greater risk of depression, with a lifetime prevalence almost twice that of men [33]. Among women, severe obesity (body mass index greater than 40) is strongly associated with depression [34]. Lower socioeconomic status and being single are also risk factors for both genders [32].

Family history of psychopathology, affective disorders in general, and major depression are particularly robust risk factors. MDD is two to four times more common among persons with an afflicted first-degree biologic relative (a parent or sibling) than among the general population [10]. Relative risks appear to be higher for early-onset and recurrent forms [10]. However, family studies indicate that major

depression is not caused by any single gene but is a disease with complex genetic features. No specific genetic risk factor has been reliably identified and associated with the development of depression [35].

Certain neurologic disorders are risk factors, such as Parkinson disease, stroke, multiple sclerosis, and seizure disorders. Among persons with certain general medical conditions, such as cancer, diabetes, myocardial infarction, or stroke, 20% to 25% will go on to experience a major depressive episode (MDE) [22]. Chronic pain, medical illness, and persistent or severe psychosocial stress elevate the risk of MDD [32].

Risk factors for late-onset depression include widowhood, physical illness, educational attainment less than high school, impaired functional status, and heavy alcohol consumption [21; 36].

As noted, peripartum women are particularly vulnerable to depression. Risk factors for peripartum depression include [21]:

- Depression or anxiety during pregnancy
- Previous history of a mood disorder
- Poor social support
- Stressful life events
- Pre-pregnancy and gestational diabetes
- Fragmented or poor sleep
- Substance abuse
- Current or past abuse experiences
- Difficulty breastfeeding in the first two months postpartum

NATURAL HISTORY OF DEPRESSION

Onset of a first major depressive episode (MDE) can be triggered by a serious psychosocial stressor and is associated with a history of panic attacks and alcohol or substance use disorder [21; 37]. A prodromal syndrome of anxiety or low-grade depression symptoms may persist for several months before onset of an initial MDE. Major depression has a variable age of onset, but the mid- to late-20s is typical [10; 22].

After the initial onset of MDD, around 15% of patients have a chronic and unremitting course. An additional 35% recover but experience one or more future recurrent episodes, and roughly 50% of first lifetime onsets recover and do not have future MDE episodes [10; 37]. The risk of recurrence becomes progressively lower over time as the duration of remission increases. Preceding severe depressive episodes, younger age, and previous multiple depressive episodes increase the risk of recurrence [10].

Antidepressant medication can alter the disease course by reducing relapse rates, while premature antidepressant discontinuation is associated with marked increases in risk of relapse [38; 39; 40]. Relapse prevention is a clinical priority, and a collaborative care model with ongoing pharmacotherapy and/or psychotherapy and regular follow-up can improve treatment adherence and reduce the risk of depressive relapse [21; 41]. A single episode of major depression is associated with a 50% chance of a subsequent episode, two episodes with a 70% chance, and three or more episodes with a 90% chance [42]. A greater number of depressive episodes predicts poor treatment response [22].

Depression is an illness with a potentially fatal outcome. Among persons with a mood disorder, 12% to 20% will ultimately die by suicide. The first three months is the period of highest risk for a first attempt, with the three months following the first attempt being the highest risk period for a second attempt [43].

DEFINITIONS

Several similar but distinct terms are used to describe depression. The DSM-5-TR states the common feature of depressive disorders is the "presence of a sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect a person's ability to function" [10]. Depressive disorder is an umbrella term that includes MDD (including major depressive episode), persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depres-

sive disorder. A new diagnosis, disruptive mood dysregulation disorder (a chronic, severe, persistent irritability), is included in the DSM-5-TR to address concerns of potential overdiagnosis and treatment of bipolar disorder in children 12 years of age and younger [10]. MDD, formerly called major depression or clinical depression, is the classic condition in this group of disorders, characterized by discrete episodes of at least two weeks' duration involving clear-cut changes in affect, cognition, and functioning, with inter-episode remissions [10]. Persistent depressive disorder is a chronic, lower-grade depression that does not have the level of severity of MDD. A depressed mood (i.e., feeling sad) that occurs for most of the day, for more days than not, and for at least two years (or at least one year for children and adolescents) is the essential feature of this disorder [10].

PATHOPHYSIOLOGY OF DEPRESSION AND SUICIDE

PATHOPHYSIOLOGY OF DEPRESSION

The understanding of MDD pathophysiology and treatment is substantially changing. Until recently, the explanatory model of depressive illness and antidepressant drug efficacy was the monoamine hypothesis. Modern antidepressants were introduced in the 1950s following serendipitous discovery of anti-depressant effects with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Selective serotonin reuptake inhibitors (SSRIs) were introduced in the late 1980s, followed by atypical antidepressants and serotonin-noradrenaline reuptake inhibitors (SNRIs) [44]. The monoamine hypothesis, proposed to explain the unexpected effects of TCAs/MAOIs in the 1950s, posits that depression results from deficient brain serotonin (5-HT) and/or norepinephrine levels. This remained the dominant paradigm of depression and the basis of nearly all FDA-approved antidepressants for the next five decades [45; 46]. Limitations of the monoamine hypothesis and mechanistic homogeneity of standard antidepressants are now understood. MDD is vastly more complex and diverse than previously assumed, and novel pathways that underlie its pathophysiology have been identified [47; 48].

Inflammatory Pathways

"Inflammation" broadly describes immune-related processes within the body, a protective immunovascular response involving immune cells, blood vessels, and molecular mediators. Inflammatory response is activated by external (microbial infection) or internal (atherosclerosis) causes to maintain homeostasis, by eliminating initial cause of injury, clearing dead and damaged cells, and initiating tissue repair. A normal immune system produces pro- and anti-inflammatory mediators. When anti-inflammatory mediators cannot inhibit the pro-inflammatory immune response, a chronic inflammatory state may develop. Acute inflammation is adaptive (for clearing infection), but chronic inflammation is usually maladaptive and destructive and may persist for years as a low-grade state without clinical symptoms [49].

An inflammatory response produces prostaglandins, white blood cells, and cytokines that generate other inflammatory molecules, including tumor necrosis factor-alpha, interleukins, and C-reactive protein. These mediators communicate with other immune system elements. Central nervous system (CNS) inflammation (neuroinflammation) involves diverse cell types, microglia, and astrocytes that both induce and limit brain inflammatory processes [49]. Peripheral and central immune systems communicate through bidirectional pathways [50]. Inflammation is a core component of chronic mood disorders.

Early-Life Adversity

Early-life adversity (ELA) describes childhood trauma, abuse, or caregiver abandonment, and research demonstrably links ELA with inflammation and later depression. The brain and immune system are incompletely formed at birth; maturation is shaped by interaction with the postnatal environment. ELA can affect immune development, which can adversely affect development of brain regions involved in mood, cognition, and behavior [50].

ELA can also promote neuroendocrine, physiologic, behavioral, and psychologic changes that impair normal development of brain systems involved in learning, motivation, and stress response. A chronically over-reactive stress response system can impair stress response, emotional regulation, and impulse control in adulthood—a biologic priming for later depression [51; 52; 53; 54; 55]. The neurobiologic correlates of ELA and inflammation are striking, and impact on adverse clinical outcomes is demonstrated across psychiatric disorders [56].

Depression as Systemic Illness

More than 80% of patients with depression have medical comorbidity, and depression is viewed as a systemic illness [57]. Chronic inflammatory states and hyper-reactive immune response to stress in patients with MDD and ELA likely contribute to the high prevalence of inflammatory medical disorders in this population. The relationship between inflammation, inflammatory disorders, and depression is bidirectional; as these medical disorders persist, the chronic inflammatory state promotes the onset of depression [58; 59].

Patient-Treatment Matching

The limitations of standard pharmacotherapy for MDD have prompted efforts to identify patient subtypes for effective treatment matching. In a 2017 study, functional magnetic resonance imaging (fMRI) brain scans of 1,200 patients with MDD were analyzed and four unique biotypes (subtypes), distinct by patterns of abnormal functional connectivity in limbic and frontostriatal networks, were identified. For example, patients with biotype 1 showed severely impaired connectivity in brain regions that regulate fear-related behaviors and reappraisal of negative emotional stimuli. Treatment response to repetitive transcranial magnetic stimulation differed by subtype and was predicted with very high accuracy [60].

ASSESSMENT AND DIAGNOSIS OF DEPRESSION

As noted, depression is a disorder of mood involving disturbances in emotional, cognitive, and behavioral regulation. The mood disorder is considered secondary if it occurs in association with substance abuse or withdrawal and/or certain medications. The mood disorder is called primary if it does not occur in association with these conditions. Primary mood disorders are categorized into depressive (unipolar) and manic depressive (bipolar) conditions. Unipolar mood conditions are divided into MDD and persistent depressive disorder [21].

Biologic measures of depression are not available for clinical practice, and diagnosis is made through psychometric findings, fulfillment of diagnostic criteria, patient history, and clinical impression [61].

SIGNS AND SYMPTOMS OF DEPRESSION

Depression is often difficult to diagnose because patient presentation is diverse, and a mood disorder may not be obvious. Patients with MDD may not seek help for mood problems, but their presentation can reflect current depression. Presentations associated with depression in patients not complaining of depressed mood or anhedonia include [10; 62]:

Clinical Factors

- Previous personal or family history of depression
- Psychosocial adversity (divorce, domestic violence)
- High healthcare system utilizers
- Chronic medical conditions (especially cardiovascular disease, diabetes, neurologic disorders)
- Other psychiatric conditions
- Times of hormonal challenge (e.g., peripartum)

Symptom Factors

- Unexplained physical symptoms
- Chronic pain
- Fatigue
- Anxiety
- Substance abuse
- Weight gain or loss
- Sleep disturbance
- Dampened affect
- Complaints about memory, concentrating, making decisions

Assessment of the presence of depression can also be made through signs and symptoms of the following cognitive, affective, and behavioral domains [10; 21; 22].

Appearance and Affect

Although most patients with MDD appear normal upon initial presentation, patients with severe symptoms can exhibit poor grooming and hygiene and changes in weight from previous contact. Psychomotor retardation may be present, reflected by a slowing or absence of spontaneous movement, flat affect, and sighs and long pauses. This represents a diminished reactivity in emotional expression. Some patients with MDD may display psychomotor agitation, reflected by pacing, hand wringing, or hair pulling [10; 21; 22; 507].

Mood and Thought Process

Patients may appear tearful or sad and often report a dysphoric mood state expressed as sadness, heaviness, numbness, or irritability and mood swings, as well as a loss of interest or pleasure in their recreational or leisure activities, difficulty concentrating, or loss of energy and motivation. Feelings of worthlessness, hopelessness, helplessness, or other negative thoughts may pervade their thinking, and ruminative thinking is not uncommon in MDD. Eye contact may be absent [10].

In the context of MDD, psychotic thought processes are congruent in content with the patient's mood state, examples being delusions of worthlessness or progressive physical decline. Evidence of psychotic symptoms requires careful assessment to rule out other contributing conditions such as bipolar disorder, schizophrenia or schizoaffective disorder, substance abuse, or organic brain syndrome [10; 22; 507].

Cognition and Sensorium

Poor memory or concentration is a frequent complaint of patients with MDD, but actual cognitive deficits are infrequent and when present may represent pseudodementia. A fluctuating or depressed sensorium suggests delirium, and the patient should be evaluated for organic contributors [21; 22; 507].

Speech

Speech in patients with MDD may be normal, slow, monotonic, or lacking in spontaneity and content. Pressured speech and racing thoughts are suggestive of mania, and disorganized speech may reflect psychosis [10; 21; 22; 507].

Thought Content, Suicidality, and Homicidality

The thought content of patients with depression is usually consistent with the dysphoric mood and should always be assessed for hopelessness, suicidal ideation, or homicidal/violent ideation or intent. Previous suicide attempts or violence predicts future behavior, and command hallucinations are associated with increased suicidal and homicidal actions [21].

SCREENING

As of 2023, the U.S. Preventive Services Task Force recommends depression screening in the adult population, including pregnant and postpartum women and older adults (i.e., 65 years of age or older). Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up [63].

The U.S. Preventive Services Task Force recommends screening for depression in the adult population, including pregnant and postpartum persons, as well as older adults.

(https://jamanetwork.com/journals/jama/fullarticle/2806144. Last accessed June 18, 2026.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

The recommendation applies to adults 19 years of age or older who do not have a diagnosed mental health disorder or recognizable signs or symptoms of depression or suicide risk. The recommendation focuses on screening for MDD and does not address screening for other depressive disorders (e.g., minor depression, dysthymia) [63].

Depression screening instruments are used to identify patients who should undergo a fuller assessment for depressive disorders [64]. The Patient Health Questionnaire-2 (PHQ-2) is a two-question screen widely recommended for use in primary care [65]:

- ''In the past two weeks, have you been bothered by little interest or pleasure in doing things?''
- ''In the past two weeks, have you been feeling down, depressed, or hopeless?''

An answer of ''yes'' to either question requires a more detailed assessment.

The Patient Health Questionnaire-9 (PHQ-9) is the most-recommended instrument following a positive screen. It consists of nine questions that ascertain depressive symptoms and symptom severity in the past two weeks and takes two minutes to complete. The PHQ-9 is recommended for use to measure severity before treatment and for periodic use during therapy to help assess response [64; 66].

Positive response to the last item ("Thoughts that you would be better off dead or of hurting yourself in some way?") is associated with increased risk for suicide attempt [67].

Other screening and assessment tools are more complex, and others have extensive use in research. Some may be useful in assessing comorbid conditions or in differential diagnosis. They include [21; 64; 68; 69; 70]:

- Zung Self-Rating Depression Scale: A widely used depression measure.
- Beck Depression Inventory II (BDI-II): Widely used as a depression outcome measure in research and practice.
- Geriatric Depression Scale (GDS): Developed to assess depression in older adults.
- Hamilton Rating Scale for Depression (HAM-D or HDRS): Extensively used in clinical research.
- Montgomery-Åsberg Depression Rating Scale (MADRS): Greater sensitivity to medication or other treatment response than the HAM-D.
- Edinburgh Postnatal Depression Scale (EPDS): The most widely used assessment tool for postpartum depression, administered to patients six weeks after delivery.
- CAGE Questionnaire:
  - Recommended due to high rates of excessive alcohol and substance use in depression. Use to screen patients undergoing further evaluation. Ask the patient if they have ever: Felt you ought to cut down on your drinking (or drug use)?
  - Had people annoy you by criticizing your drinking (or drug use)?

  - Felt bad or guilty about your drinking (or drug use)?
  - Had a drink (or drug use) as an eye opener first thing in the morning to steady your nerves or get rid of a hangover or to get the day started?
- Each affirmative response earns one point. One point indicates a possible problem. Two points indicate a probable problem.
- The Distress Thermometer: Developed for patients with significant language or communication difficulties, this one-question screen identifies distress from any source. The person marks a scale that asks: "How distressed have you been during the past week on a scale of 0 to 10?" Scores of 4 or more indicate significant distress that requires further investigation.

ASSESSMENT

As noted, a positive screen may indicate the presence and severity of depression, but it does not provide the clinical information required for diagnosis and treatment. Additional psychologic testing with the Millon Clinical Multiaxial Inventory-III (MCMI-III) or Minnesota Multiphasic Personality Inventory-2 (MMPI-2) can help determine diagnosis or differential diagnoses [71]. Both instruments should only be interpreted by licensed psychiatrists or psychologists with training in psychologic testing and assessment. Assessing for self-harm is also important. Persons who survive a serious suicide attempt may sustain injuries such as broken bones, brain damage, or organ failure and often experience continued depression and other mental health problems [72; 73].

An appropriate patient history includes information about the present illness, the medical history and medication history, including any substance abuse or dependence [21]:

- History of present illness: Determine onset, severity, prior history, concurrent psychiatric conditions, and psychosocial stressors
- Medical history: Rule out medical disorder cause of major depression
- Medication history and substance use disorder

According to the American Psychiatric Association, patients should receive a thorough diagnostic assessment in order to establish the diagnosis of major depressive disorder, identify other psychiatric or general medical conditions that may require attention, and develop a comprehensive plan for treatment.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed June 18, 2026.)

Strength of Recommendation: I (Recommended with substantial clinical confidence)

DIAGNOSIS OF DEPRESSION

In 2013, the American Psychiatric Association (APA) published their most recently revised diagnostic criteria for depression and other psychiatric illness in the DSM-5, including major depression (i.e., MDD) [10]. The DSM-5 underwent a text revision in 2022, with the addition of prolonged grief disorder and new symptom codes that allow clinicians to indicate the presence or history of suicidal behavior and nonsuicidal self-injury.

As stated, the DSM-5-TR umbrella of depressive disorders includes MDD (including major depressive episode), persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, unspecified depressive disorder, and disruptive mood dysregulation disorder, a new diagnosis added to address concerns about the potential overdiagnosis of and treatment for bipolar disorder in children up to 12 years of age [10].

Persistent Depressive Disorder

Persistent depressive disorder is a depression of less severity than MDD that usually begins in childhood and adolescence. The depressed mood lasts for most of the day, for more days than not, must be present for at least two consecutive years (at least one year in children and adolescents), and must include the presence (while depressed) of two or more of the following symptoms [10]:

- Poor appetite or overeating
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self-esteem
- Poor concentration or difficulty making decisions
- Feelings of hopelessness

Major Depressive Disorder

To meet the diagnosis of MDD, a person must have at least five of the following symptoms for at least two weeks' duration and represent a change from previous functioning. At least one of the symptoms must be either depressed mood or loss of interest or pleasure [10]:

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all or almost all activities most of the day or nearly every day
- Significant weight loss or gain (>5% body weight) or increase or decrease in appetite
- Insomnia/hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue/loss of energy nearly every day
- Feelings of worthlessness or inappropriate guilt nearly every day
- Diminished concentration or indecisiveness nearly every day
- Recurrent thoughts of death or suicide, suicide attempt, or a specific plan for attempting suicide

In addition, the symptoms must not meet the criteria for a mixed episode. The patient with MDD has never experienced a manic, mixed, or hypomanic episode. Symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Additionally, the symptoms may not be due to the direct physiologic effects of a recreational or prescribed drug or be better accounted for by bereavement (i.e., after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation) [10].

The diagnostic symptoms of MDD represent the domains of affective, behavioral, cognitive, and somatic impairment. Affective or mood symptoms include depressed mood and feelings of worthlessness or guilt, while behavioral symptoms include social withdrawal and agitation. Cognitive symptoms include difficulties with concentration or decision making, and somatic or physical symptoms include insomnia or fatigue.

The DSM-5-TR diagnostic criteria for MDD also include several specifiers to further describe the nature of the current episode of MDD. These specifiers include [10]:

- Anxious distress
- Mixed features
- Melancholic features
- Atypical features
- Mood-congruent psychotic features
- Mood-incongruent psychotic features
- Catatonic features
- Peripartum onset
- Seasonal pattern

Criteria for Anxious Distress Specifier

In order for a patient with MDD to be classified as meeting the criteria for anxious distress, he or she must have at least two of the following symptoms during the majority of days [10]:

- Feeling keyed-up or tense
- Feeling unusually restless
- Having difficulty concentrating due to worry
- Fearing that something awful may happen
- Worrying about losing control

High levels of anxiety are associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse. It is therefore clinically useful to accurately specify the severity level of anxious distress:

- Mild: Two symptoms
- Moderate: Three symptoms
- Moderate-to-severe: Four or five symptoms
- Severe: Four or five symptoms, with motor agitation

Criteria for Mixed Features Specifier

MDD with mixed features is a significant risk factor for the development of bipolar I or II disorder. A patient with MDD may be classified as meeting the criteria for mixed features when at least three of the following manic/hypomanic symptoms are present during the majority of days of a depressive episode [10]:

- Elevated, expansive mood
- Inflated self-esteem, grandiosity
- More talkative than usual or feeling pressure to continue talking
- Ideas, thoughts are racing
- Increase in energy or goal-directed activity
- Increased or excessive involvement in activities with high potential for painful consequences
- Decreased need for sleep

Criteria for Melancholic Features Specifier

For a patient with MDD to be classified as meeting the DSM-5-TR criteria for melancholic features he or she must have either a loss of pleasure in all, or almost all, activities or a lack of reactivity to usually pleasurable stimuli (i.e., does not feel much better, even temporarily, when something good happens). In addition, three (or more) of the following symptoms must be present [10]:

- Distinct quality of depressed mood (e.g., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)
- Depression regularly worse in the morning
- Early morning awakening (at least two hours before usual time of awakening)
- Marked psychomotor retardation or agitation
- Significant anorexia or weight loss
- Excessive or inappropriate guilt

Criteria for Atypical Features Specifier

Mood reactivity (i.e., mood brightens in response to actual or potential positive events) is the characteristic feature of MDD with atypical features. In addition, at least two of the following symptoms must be present [10]:

- Significant weight gain or increase in appetite
- Hypersomnia
- Leaden paralysis (i.e., heavy, leaden feelings in arms or legs)
- Long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment

Essentially, atypical MDD is characterized by vegetative symptoms of reversed polarity (e.g., increased rather than decreased sleep, appetite, weight), marked mood reactivity, hypersensitivity to rejection, phobic symptoms, or a sense of severe fatigue that creates a sensation of leaden paralysis or extreme heaviness of the extremities [22; 507].

Criteria for Mood-Congruent Psychotic Specifier

According to the DSM-5-TR, MDD with psychotic features includes the presence of delusions and/or hallucinations. Specifically, with mood-congruent psychotic features, the content of all delusions/hallucinations is consistent with the typical depressive themes (i.e., personal inadequacy, guilt, disease, death, nihilism, deserved punishment) [10].

Criteria for Mood-Incongruent Psychotic Specifier

The criteria for MDD with mood-incongruent psychotic features is satisfied when the content of delusions/hallucinations does not involve typical depressive themes or the content is a mix of mood-incongruent and mood-congruent themes [10].

Criteria for Catatonia Specifier

The specifier for catatonia can apply to an episode of depression if catatonic features are present during most of the episode. The clinical picture of the catatonic type of MDD is dominated by at least three of the following [10]:

- Stupor (i.e., motoric immobility; not actively relating to environment)
- Catalepsy (i.e., passive induction of a posture held against gravity)
- Waxy flexibility (i.e., slight, even resistance to positioning by examiner)
- Mutism (i.e., no, or very little, verbal response)
- Negativism (i.e., opposition or no response to instructions or external stimuli)
- Posturing (i.e., spontaneous and active maintenance of a posture against gravity)
- Mannerism (i.e., odd, circumstantial caricature of normal actions)
- Stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements)
- Agitation, not influenced by external stimuli
- Grimacing
- Echolalia (i.e., mimicking another's speech)
- Echopraxia (i.e., mimicking another's movements)

Criteria for Peripartum Onset Specifier

Mood episodes can have their onset either during pregnancy or postpartum. Between 3% and 6% of women will experience the onset of a major depressive episode during pregnancy or in the weeks or months following delivery. Fifty percent of "postpartum" major depressive episodes actually begin prior to delivery [10]. Thus, these episodes are referred to collectively as peripartum episodes. Peripartum-onset mood episodes can present either with or without psychotic features. Postpartum mood (major depressive or manic) episodes with psychotic features appear to occur in from 1 in 500 to 1 in 1,000 deliveries. After a woman has had a postpartum episode with psychotic features, the risk of recurrence with each subsequent delivery is between 30% and 50%. This specifier may be applied to a current episode of MDD if the onset is within four weeks postpartum [10].

Criteria for Seasonal Pattern Specifier

According to the DSM-5-TR, MDD with seasonal pattern specifier can be applied to the pattern of major depressive episodes in MDD, recurrent. The essential feature is the onset and remission of major depressive episodes at characteristic times of the year. Criteria include [10]:

- A regular temporal relationship between the onset of MDD and a particular time of the year (e.g., fall, winter)
- Full remissions (or a change from MDD to mania or hypomania) at a characteristic time of the year (e.g., depression disappears in the spring)
- In the last two years, two MDD episodes have occurred that demonstrate the temporal seasonal relationships defined above and no nonseasonal major depressive episodes have occurred during that same period.
- Seasonal MDD episodes substantially outnumber the nonseasonal MDD episodes that may have occurred over the individual's lifetime.

Bereavement and Prolonged Grief Disorder

With bereavement, the loss of a loved one is a particularly severe stressor. Bereavement is commonly accompanied by the signs and symptoms of MDD, with roughly 25% of bereaved persons exhibiting a diagnosable major depression at two months and seven months following the loss [74]. The death of a loved one is followed by an intensely emotional and disruptive period that gradually attenuates as the death is comprehended and accepted and its consequences understood (integration). It is a highly stressful period accompanied by the need to attend to a range of things not usually on one's agenda. Most people meet the coping demands and are able to find a pathway through the sorrow, numbness, and even guilt and anger that are part of the normal grieving process. A small minority, however, do not cope effectively. For them, the feelings of loss become debilitating. They do not improve with the passing of time and can become so long-lasting and severe that recovering from the loss and resuming a normal life is impossible without assistance [75]. These people are suffering from prolonged grief disorder, a syndrome in which healing is impeded and acute grief is intense and prolonged. Individuals with more severe and prolonged major depressive manifestations tend to be younger with a history of previous episodes of major depression, and antidepressant medications or psychotherapy should be used in cases with prolonged depressive reaction with significant functional impairment [10; 507].

Prolonged grief disorder is the newest disorder to be added to the DSM. The disorder was added to the DSM-5-TR in 2022 after several decades of studies that suggested many people were experiencing persistent difficulties associated with bereavement that exceeded expected social, cultural, or religious expectations [10]. Prolonged grief disorder often co-occurs with other mental disorders (e.g., PTSD, anxiety, depression). Sleep problems, such as poor long-term sleep, occur in an estimated 80% of people with this disorder [501].

Prolonged grief disorder is defined as "intense yearning or longing for the deceased (often with intense sorrow and emotional pain) and preoccupation with thoughts or memories of the deceased. In children and adolescents, this preoccupation may focus on the circumstances of the death" [10]. In adults, this intense grief must still be present one year after a loss to be considered prolonged grief disorder; in children, the timeframe is six months. Additionally, the individual with prolonged grief disorder may experience significant distress or problems performing daily activities at home, work, or other important areas [10]. It is important for clinicians to differentiate prolonged grief disorder from usual acute grief, as well as depression and anxiety disorders [75]. Risk factors for prolonged grief disorder include past losses, separations that can impact current losses, and a history of depressive illness [10]. Symptoms include [10]:

- Identity disruption (e.g., feeling as though part of oneself has died)
- A marked sense of disbelief about the death
- Avoidance of reminders that the person is dead
- Intense emotional pain (e.g., anger, bitterness, sorrow)
- Difficulty reintegrating (e.g., unable to engage with friends, pursue interests, plan for the future)
- Emotional numbness
- Feeling that life is meaningless
- Intense loneliness and feeling of being detached from others

An estimated 7% to 10% of bereaved adults will experience the persistent symptoms of prolonged grief disorder, and 5% to 10% of bereaved children and adolescents will experience depression, PTSD, and/or prolonged grief disorder [501; 502]. Treatments using elements of CBT have been found to be effective in reducing symptoms [10]. Complicated grief treatment incorporates components of CBT and other approaches to help patients adapt to the loss. It focuses on accepting the reality of the loss and

on working toward goals and a sense of satisfaction in a world without the loved one [501]. Research has shown that CBT is effective in addressing sleep problems associated with prolonged grief disorder. CBT also has been shown to be superior in long-term effects to supportive counseling in children and adolescents experiencing symptoms of prolonged grief disorder [502; 503].

Bereavement support groups can provide a useful source of social connection and support. They can help people feel less alone, thus helping to avoid the isolation that could increase the risk for prolonged grief disorder. Despite the existence of effective treatments, people experiencing prolonged grief disorder may not seek help. One study of 86 bereaved caregivers with symptoms of prolonged grief disorder found that only 43% accessed mental health services [504].

ASSESSING AND DIAGNOSING DEPRESSION IN SPECIAL POPULATIONS

Healthcare providers can create a more comfortable environment for a patient of another culture by acknowledging the impact of culture and cultural differences on physical and mental health [76; 77]. Symptom presentation is influenced by cultural factors, and in some cultures, depression and anxiety may be expressed through somatic symptoms, such as musculoskeletal pain and fatigue. Providers may consider starting the conversation with the patient by focusing on physical symptoms. The concept of depression also varies across cultures, and patients may not seek medical treatment unless symptoms manifest as psychosis, conversion disorders, or significant physical ailments [78].

The assessment and treatment of major depressive disorder should consider the impact of language barriers, as well as cultural variables that may influence symptom presentation, treatment preferences, and the degree to which psychiatric illness is stigmatized.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed June 18, 2026.)

Strength of Recommendation: I (Recommended with substantial clinical confidence)

Women with somatization are more likely to indicate interest in medication and their faith as sources for mental health care. However, ethnic differences tend to be very pronounced regarding medication preferences, with ethnic minority women showing less interest in medication than White individuals born in the United States [79].

Black/African Americans

In general, Black/African Americans are more likely than White Americans to seek help for psychologic distress in the primary care settings and are more likely to believe that mental health professionals can be helpful, but also are more likely to believe mental illness will improve on its own [80]. They tend to seek services later and, therefore, face worse outcomes [81]. When they perceive they need help for an emotional problem, African American women tend to prefer individual or group therapy over medication [79].

Latinx/Hispanic Americans

Latinx/Hispanic Americans often show psychologic distress differently, and assessment for depressive symptoms alone may not adequately capture their psychologic distress [82]. Latinx/Hispanic Americans may be more likely to seek treatment for depression in primary care settings, although cultural values may be inconsistent with accepting treatment [80; 83]. Latina women are more likely to express distress via depressive symptoms while Latino men are more likely to externalize distress [82]. When they perceive they need help for an emotional problem, Latina women tend to prefer individual or group therapy over medication [79].

Asian Americans

Asian immigrants, especially Chinese Americans, are less likely to use mental health services than other ethnic groups [84]. The discrepancy between aspiration and achievement may better predict psychiatric illness and emotional disturbance than socioeconomic status [85].

Older Patients

Major depression or persistent depressive disorder (dysthymia) with an age of onset after 60 years is referred to as late-onset depression. It is characterized by a greater presence of apathy and less lifetime presence of personality pathology than depression of earlier onset. Older patients tend to exhibit more vegetative signs and cognitive disturbance and complain less of dysphoria. In this population, major depression may be misattributed to physical illness, dementia, or the aging process itself [86]. Depression in the elderly is widespread, often undiagnosed, and usually untreated. Several factors contribute to missed diagnoses of depression in the elderly, including differences in presenting symptoms, stereotyping, provider and organizational barriers, and polypharmacy [21].

In individuals with late-life depression, the American Psychiatric Association states that the identification of co-occurring general medical conditions is essential, as these disorders may mimic depression or affect choice or dosing of medications.

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Differences in Symptom Presentation

While DSM-based epidemiology studies suggest that the frequency of MDD declines with age, symptom-based assessment studies show increased rates of depression in older adults, especially women [21]. Older adults are less likely than younger adults to report feelings of dysphoria such as sadness, unhappiness, or irritability, suggesting that the standard diagnostic criteria for depression may be more difficult to apply to older adults or that older adults are disinclined to disclose such feelings [86; 87].

Similar to other subgroups, older adults with depression often present with nonspecific somatic complaints such as insomnia, appetite disturbances, lack of energy, fatigue, chronic pain, constipation, and musculoskeletal disorders [21]. Stigma also contributes to the denial among elderly patients of the psychologic symptoms of depression and refusal to accept the diagnosis. This appears to be particularly the case with older men, who also have the highest rates of suicide in later life [86; 88].

Provider-Related Factors

Provider-specific factors contributing to under-detection and under-treatment of depression include reluctance to inform older patients of a depression diagnosis due to uncertainty over the diagnosis and proper treatment, reluctance to stigmatize, concern regarding medication interactions, lack of access to psychiatric care, and doubts regarding treatment effectiveness and cost-effectiveness [89]. Additional factors are physician overconfidence in their ability to diagnose, treat, and manage depression in the absence of sufficient training and education and a presumption (based on their familiarity with the patient) that they have nothing new to learn about the patient [89; 90; 91].

Stereotyping

Healthcare professionals are not immune from harboring the stereotypes of the elderly often found among society in general. These can include attitudes that a depressive response to interpersonal loss, physical limitation, or changing societal role is an inevitable and even normal aspect of aging [89; 92; 93; 94]. The elderly may view their suicidal thoughts as age-appropriate [91]. When held by patients and family members, these erroneous beliefs can lead to under-reporting of symptoms and lack of effort on the part of family members to seek care for patients [93; 94]. When held by clinicians, these beliefs can result in delayed or missed diagnoses, less effective treatment, or suicide in the elderly patient. Studies have shown that a great majority of geriatric suicide cases have visited a physician within one month of their suicide [89; 91].

Systemic Barriers

The healthcare system itself has increasingly restricted the time allocated for patient care, forcing mental health concerns to compete with general medical conditions for provider attention. Primary care providers often report feeling too time-pressured to investigate depression in older patients [95].

Polypharmacy

First-episode depression in elderly patients may have an undiagnosed neurologic or other medical disorder etiology. Because some medications, such as beta-blockers, can precipitate depression in the elderly, consideration should be given to the potential role of medication side effects, particularly because this population is likely to be taking many different medications [507].

Women

As noted, women have a higher lifetime prevalence of depression and are particularly vulnerable during their childbearing years [11]. In one study, depressed women were found to mention mental symptoms when visiting a primary care provider for medical concerns (e.g., respiratory infection), giving practitioners clues as to their mental state that were not often explored [96]. Primary care providers should be alert to these clues, and screen and follow up with these women, as appropriate.

When depression develops during pregnancy, the course and presentation of the disease is often unique [19]. It is important that perinatal depression be identified and treated as early as possible to minimize the risks to the mother and fetus. Screening during the antepartum and postpartum periods should focus on signs and symptoms experienced in the previous week, utilizing a tool designed specifically for this population (e.g., the Edinburgh Postnatal Depression Scale) [97].

Children

Depression does develop in children, in some cases at a young age, and the long-term effects can be significant even after resolution of depressive symptoms [97]. There are several inherent barriers in the accurate assessment of younger children, including limited cognitive, language, and reading abilities [98]. For this reason, multiple "informants" are used to gain a clear clinical picture; however, it is important to remember that the child has the greatest knowledge regarding his or her own internal state. Several screening tools have been developed specifically for children and adolescents, but these are generally recommended for those 7 years of age and older [99; 100].

Lesbian, Gay, Bisexual, and Transgender Individuals

Some depression risk factors occur with greater frequency in gay, lesbian, bisexual, transgender, and other gender and sexual minority (LGBT+) communities, including family rejection, ostracism, bullying and peer victimization, and negative self-image, and depression is more common in this group than in the general population [101; 102]. However, there is some evidence that available screening tools may overestimate the incidence of mental disorders among LGBT+ patients [103]. Because the risk of suicide is high in this population, any possible depressive signs or symptoms should be fully explored.

DIFFERENTIAL DIAGNOSIS

Because depression can be a manifestation of other psychiatric conditions, substance use disorders, CNS disorders, general medical conditions, or medication side effects, a differential diagnosis should be performed to rule out other conditions that may account for the depression. MDD can co-occur with any medical condition, but depression can also be a biologic manifestation of certain neurologic and medical conditions. In these cases, primary depression is ruled out. Considerations for the conditions discussed in the following section should be made in the differential diagnosis [10; 104; 507].

CNS Conditions

A broad range of CNS processes and conditions can produce changes in mood, cognition, and behavior that resemble MDD. These include Alzheimer disease, Parkinson disease, Huntington disease, multiple sclerosis, stroke, and seizure disorders; neoplastic lesions of the CNS; inflammatory conditions such as systemic lupus erythematosus; sleep disorders, particularly obstructive sleep apnea; and infectious diseases such as syphilis, Lyme disease, and human immunodeficiency virus (HIV) encephalopathy.

Pharmacologic Agents

Medications that can induce mood changes include antihypertensive medications, steroids, medications that affect sex hormones, H2 histamine blockers, sedatives, muscle relaxants, appetite suppressants, and cytotoxic chemotherapy agents. Patients taking several medications are at increased risk.

Endocrine Disorders

Several endocrine disorders, including Addison disease, Cushing disease, hyper- and hypothyroidism, prolactinomas, and hyperparathyroidism, have been linked to symptoms of depression. Treatment of the underlying disease should alleviate depressive symptoms.

Other Psychiatric Conditions

Depressive symptoms or mood disturbance can be due to psychiatric conditions other than MDD. Intoxication or acute withdrawal associated with alcohol and almost all recreational drugs can disrupt mood, cognition, and behavior. Furthermore, depressive symptoms may be a phase of bipolar disorder. It is important to distinguish bipolar from unipolar depression, as treatment decisions are based on this distinction. Assessment should always involve inquiry about manic or hypomanic episodes, using the following DSM-5-TR criteria for bipolar disorder [10]:

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary)
- During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behavior:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep
  - More talkative than usual or pressure to keep talking (pressured speech)
  - Flight of ideas or subjective experience that thoughts are racing
  - Increase in goal-directed activity or psychomotor agitation
  - Excessive involvement in pleasurable or hedonistic activities with a high potential for painful consequences
- The mood disturbance sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
- The episode is not attributable to the physiologic effects of a substance (e.g., an illicit drug, a medication, other treatment) or to another medical condition

These criteria constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Other psychiatric conditions with similar presentation to MDD include seasonal affective disorder, persistent depressive disorder, anxiety disorders, eating disorders, and personality disorders, especially borderline personality disorder. Many patients with MDD who appear labile, demanding, or pathologically dependent look dramatically different after the depressive episode has been treated adequately.

COMORBID CONDITIONS

Additional psychiatric disorders are present in many patients with MDD. Comorbidity rates differ between studies conducted with community compared with clinical populations. However, the most commonly occurring psychiatric comorbidities and their rates of occurrence in persons with MDD are [22; 105; 106; 107; 108]:

- Generalized anxiety disorder (62%)
- Social phobia (52%)
- Post-traumatic stress disorder (PTSD) (50%)
- Panic disorder (48%)
- Specific phobia (43%)
- Obsessive-compulsive disorder (42%)
- Any personality disorder (30%)
- Impulse control disorders (30%)
- Substance use disorders (24%)
- Borderline personality disorder (10% to 15%)

In addition, depression and certain medical conditions co-occur at very high rates. One large clinical trial found that depressed study participants had an average of 3.3 general medical conditions, including chronic pain, diabetes, cancer, HIV, Parkinson disease, and cardiovascular disease [109]. Medical comorbidity is highest among the elderly, with very high rates of depression found in patients with stroke (30% to 60%), coronary artery disease (up to 44%), cancer (up to 40%), Parkinson disease (40%), and Alzheimer disease (20% to 40%). The recurrence rate of MDD in the elderly is also extremely high, at roughly 40% [18].

Pseudodementia

Cognitive impairment often accompanies MDD. Some patients have both MDD and dementia, while others have cognitive impairment that is secondary to MDD, termed pseudodementia. Pseudodementia should resolve when MDD is successfully treated. Several clinical features help differentiate pseudodementia from true dementia. When performing cognitive tasks, pseudodemented patients generally exert relatively less effort but report more incapacity than demented patients. In the latter group, especially in the advanced stages, patients typically neither recognize nor complain of their cognitive failures, as insight is impaired. In contrast, pseudodemented patients often vehemently complain that they cannot think or remember clearly. Pseudodementia also lacks the signs of cortical dysfunction (e.g., aphasia, apraxia, agnosia) that are seen in degenerative dementia. It is essential that individuals with MDD-related cognitive disturbance not be misdiagnosed and subsequently denied aggressive treatment [507].

INITIAL TREATMENT OF DEPRESSION

Although the DSM-5-TR criteria require the presence of five of nine symptoms for MDD diagnosis, significant impairment in functioning can occur with as few as two symptoms [10; 110]. Therefore, the goal of treatment should be to achieve remission, to reduce relapse and recurrence, and to return patients to their previous level of occupational and psychosocial function. Remission is defined as the absence of depressive symptoms, response is defined as a 50% or greater reduction in symptoms, and partial response is defined as a 25% to 50% reduction in symptoms [21; 111].

An estimated 70% to 80% of antidepressants are prescribed in primary care, making it critical that clinicians understand their use and have a system that supports best practices [21]. However, evidence suggests that nonpsychiatric practitioners underdiagnose and undertreat depressive illnesses [43; 112].

Primary care clinicians who diagnose a patient with MDD face several challenges in achieving remission in the patient. These include time constraints on the treatment of a time-intensive disorder; potential comorbidities; lack of training on differential diagnoses; initial patient presentation for a medical and not a psychiatric problem; potential for poor adherence to treatment; unavailability of psychotherapy in many primary care clinics; potential discomfort among primary care providers in providing nonmedical, psychologic care; and patient expectation of a "quick fix" [43].

INITIAL COMMUNICATION WITH THE PATIENT

Patient Education

An essential aspect of treating major depression is the active engagement of patients and their families during the process. Engagement is the foundation for communication between providers and patients, and at the time of diagnosis, patient education represents a useful and important topic of communication. Patient education is also important to help counter the negative effects of pessimism, low motivation, low energy, social isolation, and guilt on treatment engagement and adherence [21; 507].

Diagnosis, prognosis, and treatment options should be addressed in patient education, which should also include a discussion of the costs, duration, side effects, and expected benefits of treatment. Patients should be reassured that depression is a medical condition, not a character defect, and recovery is the rule, not the exception [21; 22; 507]. Treatment is effective for many patients, and it is important to stress the treatment goal is complete remission—not just getting better but staying well. However, the risk of recurrence is high (50% after one episode, 70% after two episodes, and 90% after three episodes), and patients and family members should be alert to early signs and symptoms of depression recurrence and seek treatment as soon as possible if depression returns [42]. Clinicians should include the following topics related to treatment and follow-up in discussions with the patient before directly addressing specific therapy options [21; 22; 507]:

- The causes, symptoms, and natural history of major depression
- Treatment options and the process of finding the best fit for each patient
- Information on what to expect during the course of treatment
- How to monitor symptoms and side effects
- The desired follow-up protocol, such as office visits and/or telephone contacts
- Early warning signs of relapse or recurrence
- The duration of treatment
- Communication with the provider
- The frequency of visits
- Patient expectations and beliefs in the controllability of their depressive symptoms

Patient Self-Management

Self-management refers to patient ability to manage treatment, lifestyle modifications, and associated physical and psychosocial challenges necessary to better ensure recovery from depression. Supported self-management typically includes action planning to change behavior. Techniques include behavioral activation, communication skills, emotion coping skills, patient education, healthy lifestyle, relapse-prevention planning, skill development, and self-monitoring. Effective self-management reduces patient reliance on healthcare providers and increases empowerment and self-efficacy [62; 113].

Behavioral Activation

Patients can be instructed to increase their daily involvement in pleasant activities and positive interactions with the environment as one of the aspects of their overall recovery plan [114]. Behavioral activation is appealing to patients in that it is simple and easily taught, effective in reducing milder depression, and can be continued following the conclusion of therapy. Behavioral activation can also be used in difficult-to-treat populations, such as depressed dementia patients. Among the elderly, regular outings and get-togethers, participation in a senior day care program, or available nursing home activities can reduce depression [21; 115; 116]. Results of a

2010 meta-analysis suggest that among patients with mild or subclinical depression, antidepressants may be no better than placebo, and that behavioral activation plus lifestyle modifications alone may offer sufficient symptom reduction [117].

Physical Activity

A robust body of evidence indicates that physical activity at a dose consistent with public health recommendations can lessen or alleviate symptoms of depression. Exercise therapy is very beneficial to patients with major depression, but the exercise must be continued over time to provide maximum benefit. Greater antidepressant effects occur when training continues beyond 16 weeks. Walking is a good initial option for many patients, and physically healthy adults should be encouraged to set a goal of 30 minutes of moderate-intensity aerobic exercise, three to five days per week [21].

DEVISING A TREATMENT PLAN

The two primary treatment options for most patients with MDD are psychotherapy and pharmacotherapy [111]. Evidence-based guidelines recommend that the process of treatment selection involve shared decision making between provider, patient, and family members, and that the values, priorities, and goals of the patient be included in discussions of risks and benefits of treatment options [118]. Ongoing communication with other providers involved in the care of a patient is essential for coordination and monitoring and can involve different care providers in the same primary care clinic or the primary care provider and therapist or psychiatrist [22; 507].

Combining pharmacotherapy and psychotherapy treatments should be considered for patients with MDD when practical, feasible, available, and affordable. Both approaches combined show better outcomes than either as monotherapy. When unable to combine therapy because of patient preference or problems with availability or affordability, consider psychotherapy when the presentation is mild-to-moderate, and antidepressants when depression is severe or chronic [21]. Patients with MDD with psychotic features should receive an antipsychotic and an antidepressant medication or electroconvulsive therapy (ECT). Lithium can be added in patients unresponsive to antipsychotic/antidepressant therapy [22; 507]. Other specific factors should be considered in treatment planning, including the presence of substance abuse, specific features, and other comorbid disorders. If a patient displays signs of potential suicide, increasing the treatment intensity, including hospitalization if needed, should be considered, and pharmacotherapy and psychotherapy should both be provided [22; 507; 508].

Alcohol or Substance Abuse/Dependence

With active substance abuse, detoxify the patient before antidepressant initiation when possible. Identifying patients who require antidepressants following the initiation of abstinence is difficult, because ongoing substance abuse can cause or amplify depressive symptoms that will dissipate with abstinence. Factors suggestive of benefit from early medication initiation include a family history of MDD, patient history of depression preceding alcohol or other substance abuse, or a history of significant depression during periods of abstinence. Use of some drugs of abuse, especially stimulants, may create a toxic interaction with monoamine oxidase inhibitors (MAOIs), and benzodiazepines and other sedative-hypnotics should be used with great caution, except as part of a detoxification regimen [22].

Specific Features

As discussed, patients with MDD may present with features that specify the current episode as catatonic, melancholic, or atypical. Rapid alleviation of potentially life-threatening catatonia in patients with MDD with catatonic features may be necessary with intravenous lorazepam or amobarbital. ECT should be considered immediately in unresponsive patients. Initiation of antidepressant medication should also begin, and catatonic patients given antipsychotic medication should be monitored for neuroleptic malignant syndrome [22; 508].

Many treatment studies in symptom-based MDD subtypes (e.g., melancholic, atypical, anxious depression) have compared an active drug to placebo. Some report efficacy, but few have evaluated preferential subtype response [119; 120].

Comorbid Psychiatric Disorders

Both depressive and anxiety symptoms respond to antidepressant medication treatment, although SSRIs and TCAs may initially worsen anxiety symptoms. Benzodiazepines may be needed as short-term adjunctive therapy but should not be used as monotherapy. Clomipramine and sertraline are efficacious in managing obsessive-compulsive symptoms; all antidepressants should be initiated at a low starting dose [22].

Patients with MDD and comorbid personality disorders, especially borderline personality disorder, poorly respond to standard antidepressants, and MAOIs should not be used in patients with borderline personality disorder [22]. Psychodynamic psychotherapy may be beneficial in modifying the personality disorder in selected patients, although antisocial personality traits often interfere with treatment adherence and the psychotherapeutic relationship [22]. Other evidence suggests that comorbid personality disorders in patients with depression interfere with treatment response to interpersonal psychotherapy but not cognitive-behavioral therapy (CBT) [121].

Eating disorders can co-occur with depression. CBT is suggested in patients with bulimia nervosa; other effective therapies include interpersonal therapy, group therapies, family therapy, and SSRIs. Bupropion should be avoided due to lowered seizure threshold, and ECT has not been shown effective [22].

If depression is identified as seasonal affective disorder, bright-light therapy is recommended as first-line therapy and can be used adjunctively with antidepressants in more severe cases. The entire range of MDD treatments may also be used for seasonal affective disorder, either combined with, or in place of, bright-light therapy [22].

Persistent Depressive Disorder and Pseudodementia

Antidepressants appear to benefit some patients with persistent subthreshold depressive symptoms (dysthymia) but lack benefit in patients with recent-onset subthreshold depressive symptoms. No clear advantage has been shown among specific antidepressants, and psychotherapy should be considered [68; 122]. For patients with persistent subthreshold depressive symptoms or depression with mild-to-moderate severity, consider an antidepressant or CBT, interpersonal therapy, or behavioral activation [68]. Unlike true dementia, cognitive impairment in pseudodementia is secondary to MDD, and should resolve with adequate antidepressant or ECT response [22].

Demographic and Psychosocial Factors Influencing the Treatment Plan

Female Sex

Some women experience mood fluctuation with gonadal hormone levels, and assessment should include a detailed assessment of mood changes across the reproductive life history. Potential drug-drug interaction should also be considered when selecting an antidepressant in women taking oral contraceptives. In perimenopausal women, SSRI and SNRI antidepressants are useful in ameliorating depression as well as in reducing somatic symptoms such as hot flashes [22].

Major Psychosocial Stressors

An MDE may follow an adverse life event, often surrounding the loss of an important relationship or life role. Antidepressant treatment decisions for MDE following such events do not differ from other contexts, but the influence of past and current psychosocial stressors on MDE severity should be considered. Adding a psychologic treatment to medication may be particularly useful [22; 507; 508]. Antidepressant medications and/or psychotherapy should be used in prolonged reaction to relationship loss with significant functional impairment, and some patients may benefit from bereavement support groups [22].

A history of early-life trauma, such as physical/sexual abuse or parental loss or abandonment, should be considered in treatment selection. A study of 681 patients with chronic MDD found that among patients with childhood trauma, CBT was consistently more effective than antidepressant monotherapy, and that combining both therapies had no significant advantage over CBT monotherapy [123]. Remission was estimated to be twice as likely with psychotherapy than antidepressants, with special benefit noted in patients with early parental loss. These results suggest a preferential response to psychotherapy in patients with chronic MDD and a history of childhood trauma [123].

An ongoing family stressor can interfere with treatment response. Ambivalent, abusive, rejecting, or highly dependent family relationships can influence development or persistence of MDD. Such families should be evaluated for family therapy, which may be used in conjunction with individual and pharmacologic therapies [22; 507].

Other Psychosocial Factors

Psychosocial stressors such as housing, food, childcare, transportation, employment, immigration status, and financial stability may be more prevalent in certain populations and should be considered during treatment planning [124]. Also, financial factors such as insurance coverage or generic versus brand name medications can affect treatment adherence. Among low-income minority women in the United States, availability of childcare and transportation are associated with significant improvement regardless of treatment modality. Medication noncompliance rates are higher in intercultural settings due to cultural expectations and communication problems [21; 125].

Cultural Factors

Essential to effective diagnostic assessment and clinical management of depression is an understanding of the cultural context of a patient's illness experience. Culture is the systems of knowledge, concepts, rules, and practices that the patient has learned over time and includes language, religion and spirituality, family structures, life-cycle stages, ceremonial rituals, customs, and moral and legal systems [10].

Ethnic minority and immigrant patients can experience many barriers to accessing mental health services, including stigma, deficits in knowledge/understanding, economic hardship, and language barriers [126]. Clinicians should take steps to address their own cultural competency when working with minority patients and ensure that all communications are clear and thorough, utilizing an interpreter when necessary. Different beliefs, values, and terms for depression will impact the perceived effectiveness of treatments. In addition, some cultures may be more likely to utilize alternative treatments (e.g., saffron) [126].

Older Age

The same factors used in therapy selection with younger patients also apply to the elderly, although treatment response may take longer to achieve [22; 507]. The starting dose of pharmacotherapy and rate of dose escalation should be carefully considered, as the elderly are more susceptible to medication side effects, especially hypotension and anticholinergic effects [22; 507]. Weight loss may be a concern for some older patients, who may benefit from medication that promotes weight gain [21].

The collaborative care approach with the elderly involves a treatment team composed of a depression care manager, primary care physician, and psychiatrist who provide a tailored approach to meet individual patient's needs and preferences. This approach is based on education, behavioral activation, antidepressants, brief problem-solving therapy, and relapse prevention [127]. Collaborative care has demonstrated considerably greater and more sustained improvement of depressive symptoms in the elderly than usual care [128].

Family History

A family history of bipolar disorder or acute psychosis indicates the need to monitor the patient for signs of bipolar disorder and treatment-emergent mania. A family history of recurrent MDD increases the likelihood of recurrent episodes and underscores the importance of maintaining treatment response. A family member with positive treatment response to a specific antidepressant offers important information to guide antidepressant selection [22].

Comorbid Medical Conditions

As with psychiatric conditions, comorbid medical conditions can impact the treatment plan for patients with depression. Pharmacologic agents should be chosen carefully in these patients due to the increased risk for adverse events and drug-drug interactions, and the following considerations are suggested [22; 507; 508]:

- Hypertension or cardiac conditions: Monitor vital signs and cardiac rhythm when treating with TCAs, SNRIs, or antidepressants with anticholinergic effects.
- Seizure disorders: Use with caution antidepressants that lower the seizure threshold, such as bupropion, clomipramine, and maprotiline.
- Parkinson disease: Serotonergic agents may worsen symptoms, and bupropion may benefit the illness but worsen psychosis if present. Selegiline may interact with L-DOPA, an agent used in the treatment of Parkinson disease.
- Obesity: Monitor for weight gain with most antidepressants.
- Sleep apnea: Choose an antidepressant with little daytime sedation.
- HIV infection: Carefully consider the potential drug-drug interactions between psychotropics and antiretrovirals.
- Chronic pain: SNRIs and TCAs are preferred over SSRIs and MAOIs.

OPTIONS FOR INITIAL THERAPY

In mild-to-moderate depression, psychotherapy can be equally as effective as medication, although with severe depression, antidepressant medication is usually necessary [129; 130]. Psychotherapy can significantly reduce symptoms, restore psychosocial and occupational functioning, and prevent relapse in patients with major depression [131]. It is especially useful in addressing the psychosocial stressors and psychologic factors that impact the development or maintenance of depressive symptoms [22; 507]. Support and education in the primary care setting are critical to improving patient adherence and follow-through with treatment. Patient factors such as the nature and duration of depressive symptoms, beliefs and attitudes toward psychotherapy, and early-life experiences (e.g., history of trauma) contribute to psychotherapy treatment response [22; 132; 507]. Patient expectations as to the outcome of therapy, particularly the expectation that treatment will lead to an improvement in symptoms, is linked to favorable therapeutic outcomes [133]. Because antidepressants and psychotherapy are both effective, careful consideration of patient preference for mode of treatment is appropriate, and a referral for psychotherapy should be given whenever psychologic or psychosocial issues are prominent or if the patient requests it [134; 135; 136].

Phases of Treatment

With the traditional three-phase model of acute, continuation, and maintenance, the distinction between continuation and maintenance phases was based on a theoretical difference between relapse (symptom recurrence before resolution of current episode) and recurrence (symptoms that constitute a new episode, after recovery from previous episode) [137; 138]. However, studies have highlighted the lack of evidence to support distinct demarcations between relapse and recurrence episodes, and a two-phase model (acute and maintenance) is now recommended [62; 139].

Acute Phase

The primary goals for the initial 8- to 24-week acute treatment phase are symptom remission, meaning that signs and symptoms of depression are absent or nearly so, and restoration of psychosocial functioning. Full symptom remission is important because residual depressive symptoms are risk factors for relapse and negative predictors of long-term outcomes. Clinicians can help patients achieve these goals through establishing a therapeutic alliance, providing patient education and self-management support, selecting appropriate treatment, and monitoring the patient for treatment response, side effects, functional status, adherence, risk of harm to self or others, and co-occurring psychiatric and medical comorbidities [43; 62; 140; 141].

Maintenance Treatment Phase

Preventing recurrence is a key goal during the maintenance phase of 6 to 24 months or longer. Clinicians should focus on healthy life strategies, personality vulnerabilities, long-term self-management, and clinical strategies to reduce recurrence and help the patient return to full functioning and quality of life. For a significant proportion of patients with MDD, maintenance pharmacologic, psychologic, complementary and alternative medicine, and neurostimulation treatments play a role in preventing recurrence. Other key clinician activities include treating comorbidities and monitoring for recurrence [62; 139; 142].

Treatment Duration

As noted, the antidepressant dose that leads to a satisfactory acute therapeutic response should be maintained during long-term treatment to prevent relapse and recurrence of depression [143; 144]. Historically, practice guidelines recommended initial treatment continuation for 6 to 12 months, but this is not supported by evidence and discontinuation decisions should not be based on treatment duration alone [145]. The two most important factors are maintaining current response and preventing relapse. Risk factors associated with chronic MDD or recurrent MDE include [62]:

- Earlier age of onset
- Severity of the initial episode (e.g., higher number of symptoms, suicidal ideation, psychomotor agitation)
- Greater number of previous episodes
- Disrupted sleep-wake cycle
- Comorbid psychopathology
- Family history of psychiatric illness
- Presence of negative cognitions
- High neuroticism
- Poor social support
- Stressful life events

The duration of untreated MDD is strongly linked to antidepressant nonresponse [62; 146].

When patients with these characteristics show substantial response or remission, the focus is helping the patient maintain their level of treatment response. When antidepressants are discontinued, have a contingency plan in place for prompt intervention if relapse occurs [38]. Early antidepressant discontinuation usually results from side effects, lack of improvement, inadequate education about the illness, failure to engage the patient during follow-up, and psychosocial factors [147; 148].

PSYCHOTHERAPY

The objective of psychotherapy (sometimes referred to as psychologic or psychosocial therapy) is to change thinking and behavior patterns, which in turn reduces emotion and stress reactivity in limbic regions and increases connectivity in limbic-cortical pathways and inhibitory control functions of prefrontal cortical regions [149]. Psychosocial treatments are preferred by many individuals with MDD, and psychotherapies can be sequenced as add-on approaches for insufficient initial antidepressant response or used as initial treatment, with antidepressants reserved for poor response to psychosocial treatment. However, many patients with more severe depression or cognitive impairment will require some degree of pharmacologic treatment to engage and maintain participation in psychotherapy [150].

The American Psychiatric Association recommends use of a depression-focused psychotherapy alone as an initial treatment choice for patients with mild-to-moderate major depressive disorder, with clinical evidence supporting the use of cognitive-behavioral therapy.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed June 18, 2026.)

Strength of Recommendation: I (Recommended with substantial clinical confidence)

Cognitive-Behavioral Therapy

CBT is a structured, circumscribed psychologic intervention that is grounded in the cognitive-behavioral model of affective disorders, which posits that irrational beliefs and distorted attitudes toward the self, the environment, and the future perpetuate depressive affects and compromise functioning [22; 507]. When CBT is used for depression, the patient works collaboratively with the therapist to identify maladaptive or self-defeating thoughts, beliefs, and interpretations and their impact on current symptoms, feelings states, and/or problem-solving abilities. Therapeutic techniques include patient education and patient-therapist collaboration to choose goals, identify unhelpful thoughts, develop experiments to challenge the accuracy of such thoughts, and identify alternative beliefs through questions that explore beliefs that exacerbate depression. Treatment incorporates structured practice outside of therapy, with scheduled activities, mood tracking, thought recording and challenging, and interpersonal skills practice. CBT can be delivered via computer software and/or by group therapy format [64].

Mindfulness-Based Cognitive Therapy

Mindfulness-based cognitive therapy integrates standard CBT with mindfulness-based skills, including mindfulness meditation, guided imagery, experiential exercises, and other techniques. The goal is to assist patients with MDD in recognizing, detaching from, and accepting negative thoughts or affect while embracing self-compassion, without necessarily attempting to change them. With practice, patients can become more detached from dysfunctional thoughts by observing them as objects [64].

Interpersonal Psychotherapy

Derived from attachment theory, interpersonal psychotherapy focuses on improving interpersonal functioning and exploring relationship patterns. It addresses the connection between patients' feelings and current relationship difficulties by targeting four primary areas: interpersonal loss, role conflict, role change, and interpersonal skills [64].

Short-Term Psychodynamic Psychotherapy

Derived from longer-term psychoanalysis and psychodynamic psychotherapy, short-term psychodynamic psychotherapy assists patients in gaining insight into unconscious conflicts as they manifest in daily life and relationships, including the therapeutic relationship (i.e., transference). This approach considers these conflicts to originate in the past, usually childhood relationships to parental figures. Patients gain insight into and work through such conflicts by exploring their feelings and therapist interpretation [64].

Marital/Family Therapy

Marital and family problems are common in mood disorders, and can predate, perpetuate, or develop as consequence to the mood disorder. Marital/family therapy approaches effective in depression treatment include behavioral approaches, problem-focused approaches, and strategic marital therapy. Marital/family therapy can be a helpful adjunct to medications and hospitalization in severely ill patients, particularly if these relationships are contributing significantly to their depression [22; 508].

Complicated Grief Therapy

Complicated grief therapy involves history-taking, psychoeducation about complicated grief and its treatment, work with memory and pictures, and imagined conversations with the deceased, over a 16-week period. In one study, adults with complicated grief were randomized to combinations of complicated grief therapy, citalopram, or placebo. Complicated grief was very much improved with complicated grief therapy; adding citalopram had no further benefit. Depressive symptoms showed greater decrease with citalopram added to complicated grief therapy; citalopram response at 20 weeks was comparable to placebo. Suicidal ideation rates showed greatest reduction with complicated grief therapy [75].

Problem-Solving Therapy

Problem-solving therapy is a time-limited, structured intervention involving therapist-patient collaboration to identify and prioritize problems; break problems down into specific, manageable tasks; problem solve; and develop appropriate coping behaviors for problems. It was developed to specifically address social problem-solving deficits common in chronic depression [151; 152]. Problem-solving therapy is designed for use in primary care settings [153; 154].

Psychotherapy Treatment Recommendations

For patients with moderate-to-severe depression, a combination of antidepressant medication and CBT or interpersonal therapy should be provided. The choice of intervention should be influenced by the duration of the episode of depression and symptom trajectory, previous course of depression and treatment response, likelihood of adherence to treatment, any potential adverse effects, and individual treatment preference and priorities [68]. A 2017 evaluation of whether CBT response was influenced by baseline depression severity suggested that patients with MDD can expect as much benefit from CBT across the wide range of illness severity [155].

For patients with persistent subthreshold depressive symptoms or mild-to-moderate depression who decline an antidepressant, CBT, or interpersonal therapy, consider counseling. Short-term psychodynamic psychotherapy should be offered to patients with mild-to-moderate depression. Individual CBT is an option for patients who have either relapsed despite antidepressant medication or have a significant history of depression and residual symptoms despite treatment and are unable or unwilling to continue antidepressant treatment. Mindfulness-based cognitive therapy should be offered to patients who are currently remitted but have experienced three or more previous episodes of depression [68].

Psychotherapy is preferred as a first-line treatment for elderly patients because of potential increased toxicity and drug-drug interactions. The evidence does not support superiority of one psychotherapy modality over another in elderly patients with MDD [64].

PHARMACOTHERAPY

Treatment with antidepressant medications can involve dosage adjustments and/or trials of a different medication at some point to maximize response and minimize side effects [22; 507; 508]. Patient adherence to the medication regimen is essential in achieving the maximum clinical benefit. Patient education regarding the treatment plan should include when and how often to take medication; the anticipated two- to four-week lag before beneficial effects may be noticed; the need to continue medication even after feeling better; what to do if problems arise; and the importance of tapering antidepressants before discontinuing them [22; 508]. Strategies to enhance adherence are discussed below. Providers should closely monitor patients for worsening depressive symptoms and emergent suicidality; appropriate intervention includes stopping or modifying the drug therapy or hospital admission [21]. Providers should instruct patients and caregiver(s) to be alert for emerging agitation/irritability, suicidality, and worsening depression, and to report this immediately to a healthcare provider [21].

An antidepressant medication is indicated for initial treatment of patients with mild to moderate depressive disorder. The effectiveness of antidepressants is comparable between and within classes of medications, including TCAs, SSRIs and other second-generation agents (e.g., SNRIs, bupropion), and MAOIs. Selection of a second-generation antidepressant is often recommended for initial treatment due to quality of published data, side effect profile compared to TCAs and MAOIs, and relative safety [21; 22; 156]. The choice of medication should be based on the following considerations: patient preference; nature of prior patient or family member response to medication; safety, tolerability, and anticipated side effects; co-occurring conditions and potential drug-drug interactions; cost [21; 22; 508]. For most patients, a SSRI, a SNRI, mirtazapine, or bupropion is optimal for initial therapy. The use of MAIOs should be restricted to patients who do not respond to other treatments [21; 22].

RECOMMENDATIONS FOR MDD SPECIFIERS AND DIMENSIONS	
Specifier or Dimension	**Recommended Agent(s)**
Anxious distress	Antidepressants with efficacy in generalized anxiety disorder (SSRIs, SNRIs, and bupropion comparable in efficacy)
Mixed features	Lurasidone Asenapine Quetiapine Aripiprazole Ziprasidone
Melancholic features	TCAs SNRIs
Atypical features	MAOIs (superior to TCAs in older studies)
Psychotic features	Antipsychotic-antidepressant combinations
Catatonic features	Benzodiazepines
Seasonal pattern	SSRIs Agomelatine Bupropion Moclobemide
Cognitive dysfunction[a]	Vortioxetine (highest efficacy) Bupropion Duloxetine Modafinil Moclobemide
Sleep disturbance[a]	Agomelatine (highest efficacy) Mirtazapine Quetiapine Trazodone (high rates of somnolence and daytime sedation)
Fatigue[a]	Bupropion (highest efficacy) SSRIs
Low energy[a]	Duloxetine
Neuropathic pain and fibromyalgia[a]	Duloxetine (highest efficacy) Amitriptyline Other SNRIs
[a]Clinical dimension not recognized in the DSM-5-TR.	
Source: [158; 159; 160]	*Table 1*

The three most distressing side effects for patients treated with antidepressants are sleep disturbance, sexual dysfunction, and weight gain [157]. Choice of medication should be guided by knowledge of comparative side effects and patient priorities; some patients will be more concerned about sexual side effects, while for others, nausea, sleep disturbances, or weight gain may be more distressing [64]. In addition, available evidence regarding the optimal pharmacotherapeutic selection for the treatment of dimensions of depression and DSM-5-TR specifiers should be considered (***Table 1***).

Selective Serotonin Reuptake Inhibitors

SSRIs are thought to act by inhibiting serotonin transporters (SERT) that reuptake serotonin (5-HT) into the presynaptic cell, increasing 5-HT in the synaptic cleft. SSRIs have advantages of low overdose lethality and better tolerability than first-generation antidepressants, which can improve adherence. SSRIs are particularly effective in patients with obsessive-compulsive symptoms but may initially worsen anxiety or panic symptoms [21; 22; 122].

This class includes the agents fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox) (off-label for MDD), citalopram (Celexa), escitalopram (Lexapro), and vortioxetine (Trintellix). Escitalopram may have fewer drug-drug interactions than other SSRIs, and fluoxetine may be a better choice in patients with poorer adherence due to its long half-life [21; 22; 122].

Common Side Effects

The most common side effects with SSRIs are gastrointestinal (nausea, vomiting, and diarrhea), activation/insomnia (restlessness, agitation, anxiety, akathisia, and sleep disturbances), sexual, headache, fatigue, and weight gain [21; 22; 122]. Many of these side effects dissipate over time. Sertraline is particularly associated with diarrhea, and paroxetine with weight gain [22; 122].

Multimodal Antidepressants

Vilazodone and vortioxetine are multimodal antidepressants that combine SSRI properties with other pharmacologic actions affecting monoamine and non-monoaminergic targets. Evidence does not suggest greater efficacy than SSRI/SNRIs, but these agents may improve tolerability or efficacy on specific clinical domains [161]. They are not approved for use in pediatric patients [175].

Vilazodone, approved in 2011, primarily acts as a SERT inhibitor and 5-HT1A receptor partial agonist, and modestly inhibits dopamine and norepinephrine transporters. This antidepressant may be most helpful in patients lacking response to initial SSRIs. Vilazodone must be taken with food, which increases its absorption and bioavailability by 72% [162; 163].

Vortioxetine, approved in 2013, acts through various serotonin receptors as an antagonist (5-HT3/7/1D), partial agonist (5-HT1B), or agonist (5-HT1A), and inhibits SERT. It also activates the glutamate system in the frontal cortex. Vortioxetine displays a specific clinical efficacy in the treatment of cognitive deficits associated with MDD. The most common side effects are nausea, vomiting, and constipation [161].

Serotonin-Norepinephrine Reuptake Inhibitors

SNRIs act by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. This results in an increase in the extracellular concentrations of serotonin and norepinephrine and therefore an increase in neurotransmission [21; 22; 122]. Most SNRIs, including venlafaxine (Effexor), desvenlafaxine (Pristiq), levomilnacipran (Fetzima), and duloxetine (Cymbalta), are several-fold more selective for serotonin than norepinephrine. Venlafaxine, desvenlafaxine, and levomilnacipran are not approved for use in pediatric patients [175].

Safety, tolerability, and side effect profiles of SNRIs resemble SSRIs, with the exception that the SNRIs have been associated (rarely) with sustained elevated blood pressure. SNRIs can be used as first-line agents, particularly in patients with significant fatigue or comorbid chronic pain, and have an important role as second-line agents in patients who have not responded to SSRIs [21; 22; 122].

Venlafaxine is especially beneficial in treating anxiety and panic attacks in patients with depression, and acts like an SSRI at lower doses (75 mg/day) but more like an SNRI at doses ≥150 mg/day [21; 22; 122].

Common Side Effects

SNRIs are associated with greater likelihood of increased pulse rate, dilated pupils, dry mouth, excessive sweating, and constipation [21]. Venlafaxine has a greater incidence of nausea and vomiting than SSRIs and may be associated with an increased risk for cardiovascular events [22; 122].

Tricyclic Antidepressants

TCAs are predominantly serotonin and/or norepinephrine reuptake inhibitors that act by blocking the serotonin transporter and the norepinephrine transporter, respectively, which results in an elevation of the extracellular concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. TCAs also have varying but typically high affinity for the H1 and H2 histamine receptors and muscarinic acetylcholine receptors.

As a result, they also act as potent antihistamines and anticholinergics. These properties are generally undesirable in antidepressants, however, and likely contribute to their large side effect profiles [164].

TCAs are classified by the nature of the final amine group on the side chain, with the tertiary amines amitriptyline (Elavil), clomipramine (Anafranil), doxepin (Sinequan), trimipramine (Surmontil), imipramine (Tofranil), and lofepramine (Lomont); the secondary amines nortriptyline (Pamelor), desipramine (Norpramin), and protriptyline (Vivactil);, and amoxapine (Asendin).

TCAs are comparable in efficacy to SSRIs/SNRIs, but their side effect profile makes them seldom used as first-line therapy [21; 22; 122]. TCAs may initially worsen anxiety or panic symptoms. Due to side effect potential of cardiac arrhythmia, TCAs should be used very cautiously, if at all, in patients with heart problems. Secondary amine TCAs cause less orthostatic hypotension and sedation than tertiary amines, which should be avoided in elderly patients due to the risk for orthostatic hypotension, sedation, cognitive problems, and cardiac effects. The secondary amine nortriptyline is especially effective for elderly patients with moderate-to-severe depression. Clomipramine is particularly effective in patients with obsessive-compulsive symptoms [21; 22; 122]. Use in pediatric patients is generally limited, and approval varies by agent [175].

Common Side Effects

Anticholinergic and antihistamine activity accounts for many side effects, including dry mouth, blurred vision, reduced gastrointestinal motility or constipation, urinary retention, cognitive and/or memory impairment, and increased body temperature [21; 22; 122]. Other side effects may include drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, hypersensitivity, changes in appetite and weight, sweating, sexual dysfunction, muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and arrhythmia. Tolerance to side effects often occurs if treatment is continued. Side effects may also be less troublesome if treatment is initiated with low doses and gradually increased [164; 165].

Monoamine Oxidase Inhibitors

MAOIs inhibit monoamine oxidase (MAO), an enzyme that degrades and inactivates 5-HT, norepinephrine, and dopamine. This increases monoamine levels and activity. Earlier MAOIs were irreversible MAO inhibitors, deactivating the enzyme until slowly replenished over a two-week period [166; 167]. MAOIs approved for use in adults include phenelzine (Nardil), tranylcypromine (Parnate), isocarboxazid (Marplan), linezolid (Zyvox, Zyvoxam, Zyvoxid), moclobemide (Aurorix, Manerix), pirlindole (Pirazidol) (approved for use in parts of Europe), and selegiline (Deprenyl, Eldepryl, Emsam).

Most MAOIs appear broadly effective in a range of depressive and anxiety disorders and may be more effective than other antidepressant classes in MDD with pronounced anxiety or panic symptoms [21; 22; 122]. MDD with atypical features may preferentially respond to MAOIs over other antidepressant classes. Although effective, MAOIs are rarely the first- or second-line treatment choice due to serious side effect potential from medication interactions and dietary restriction. The selegiline transdermal patch (Emsam) used at the lowest strength (6 mg delivered over 24 hours) may lack the dietary restrictions required of oral MAOIs [168]. Moclobemide is a reversible inhibitor of monoamine oxidase type A, greatly improving its safety, including overdose safety (i.e., 20,000 mg ingestion was non-fatal). This drug lacks TCA side effects or SSRI/SNRI sexual side effects; improved libido, erection, or orgasm is more commonly reported [169; 170]. Moclobemide may be superior to other antidepressants in treatment-resistant depression [171]. This drug is approved for use in Canada and throughout Europe and Asia but is not available in the United States [169].

MAOI INTERACTION TO TYRAMINE CONTENT IN FOOD		
None to Little	**Moderate**	**Severe**
Avocados Bananas Bouillon Chocolate Fresh cheeses Fresh meats Peanuts Soy milk Yeast extracts	Red wine White wine Canned beer	Aged cheeses Aged and fermented meats Broad (fava) bean pods Spoiled meats and fish Soy sauce Tap beer Smoked or pickled fish Sauerkraut
Source: [166]		*Table 2*

In general, the American Psychiatric Association recommends that the use of nonselective monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed June 18, 2026.)

Strength of Recommendation: I (Recommended with substantial clinical confidence)

Common Side Effects

With oral ingestion, MAOIs inhibit the catabolism of dietary amines. When foods containing tyramine are consumed, the individual may suffer from hypertensive crisis (***Table 2***) [166]. If foods containing tryptophan are consumed, hyperserotonemia may result. The amount required to cause a reaction varies greatly from individual to individual and depends on the degree of inhibition, which in turn depends on dosage and selectivity.

MAOIs should not be combined with psychotropic drugs or with any other psychoactive substance except under expert care. This includes a wide range of prescribed, over-the-counter, and illicit drugs and nutritional supplements, such as St. John's wort. Common side effects include orthostatic hypotension, weight gain, sexual dysfunction, sedation, headache, and insomnia [166].

Atypical Antidepressants

The atypical antidepressants are diverse in monoamine activity and do not fit the profile of other classes. They include bupropion (Wellbutrin), nefazodone (Serzone), mirtazapine (Remeron), and trazodone (Desyrel). Nefazodone and trazodone block postsynaptic serotonin type-2 receptors and inhibit presynaptic serotonin reuptake. Bupropion inhibits activity of norepinephrine and dopamine transporters, and the active metabolite hydroxybupropion contributes to the drug's effects. Mirtazapine is a potent antagonist at 5-HT2, 5-HT3, alpha2, and H1 histamine receptors. As a group, these agents show low toxicity in overdose and may have an advantage over the SSRIs by causing less sexual dysfunction and gastrointestinal distress [21; 22; 122].

Each agent has apparent benefits and drawbacks, with some better suited for specific patient populations. Bupropion is associated with a risk of seizure at higher doses, especially in patients with a history of seizure or eating disorders, and should be used cautiously in anxious patients [21; 22; 122]. It may be more effective for atypical MDD than other antidepressants. Only bupropion and trazodone are approved for pediatric use [175].

Mirtazapine can be very sedating and promotes appetite and weight increase, which in some patients may be desirable. It has a faster onset of action than fluoxetine, paroxetine, or sertraline, and may be superior to SSRIs in depression associated with severe insomnia and anxiety. Trazodone is also very sedating and is usually used as a sleep aid rather than as an antidepressant [21; 22; 122].

Common Side Effects

The side effects of atypical antidepressants vary considerably. With bupropion, the most common side effects are agitation, jitteriness, mild cognitive dysfunction, insomnia, gastrointestinal upset, and possible increased risk for seizures [122]. Patients taking mirtazapine may experience dry mouth, sedation, weight gain, and increased serum cholesterol [22]. Sedation is the most common side effect associated with trazodone, followed by cardiovascular side effects (such as orthostasis) and sexual side effects [22]. Finally, nefazodone is associated with sedation, dry mouth, nausea, constipation, orthostasis, visual alterations, and possible increased risk of hepatotoxicity have led to nefazodone being seldom prescribed [122].

CNS Stimulants

Although the role of psychostimulants for antidepressant monotherapy is very limited, they may have a role in the treatment of apathetic major depression in which apathy imperils adherence to treatment and self-care, in patients who cannot tolerate the side effects of standard antidepressants, in terminally ill and medically ill patients with depression, and in elderly patients with complicating medical conditions [10; 172; 173; 174].

This medication class includes amphetamine derivatives such as dextroamphetamine (Dexedrine, Adderal), methylphenidate (Ritalin), and modafinil (Provigil). Methylphenidate inhibits dopamine reuptake by its transporter and, to a lesser degree, norepinephrine reuptake. Dextroamphetamine increases cytosolic dopamine and norepinephrine by blocking vesicular sequestration of dopamine and norepinephrine through inhibition of vesicular monoamine transporter-2 activity [21; 22; 122].

Common Side Effects

In general, CNS stimulants are associated with side effects related to hyperarousal (e.g., agitation, aggression, tachycardia, restlessness, insomnia). Other potential side effects include headache, anorexia, nausea, and irritability [175]. Modafinil is associated with markedly lower subjective stimulation.

CNS stimulants are contraindicated in patients with a history of substance use disorder, with agitated states, and with moderate-to-severe hypertension [175]. In addition, patients who have initiated MAOIs within the last 14 days should not begin therapy with a dopamine agonist.

Pharmacotherapy to Improve Cognitive Dysfunction

Full functional recovery is the overarching therapeutic goal of MDD treatment. Cognitive symptoms of depression critically impact social, occupational, and physical functioning; often persist after mood symptoms have lessened or remitted; and elevate recurrence risk in remitted patients. Functional outcomes modestly correlate with mood symptom outcomes but are strongly influenced by persistent cognitive impairment [176; 177; 178]. Mood symptoms are a primary focus of depression assessment and treatment, and standard depression pharmacotherapies have minimal benefit on improving cognitive dysfunction.

Vortioxetine has demonstrated efficacy in improving multiple domains of cognitive function, including executive function, processing speed, attention, and learning/memory, independent of its effect on core mood symptoms [45; 179; 180]. Duloxetine can improve learning and memory in patients with MDD [181]. Lisdexamfetamine has some benefit in improving executive function, while single-dose modafinil (200 mg) significantly improved performance on tests of episodic memory and working memory in remitted MDD subjects without side effects [159; 182].

Potential Complications with All Antidepressants

Sexual Dysfunction

All commercially available antidepressants are associated with sexual side effects that can be long-lasting or permanent, even with short-term use [506]. SSRI/SNRIs show the highest rates of sexual dysfunction, including impaired sexual motivation, desire, arousal, and orgasm affecting men and women. Prescribing physicians greatly underestimate the prevalence and patient burden of sexual side effects from antidepressants and other medications [183]. Among antidepressants, prevalence rates of sexual side effects are highest with venlafaxine and SSRIs; moderate with TCAs and MAOIs; low with bupropion, trazodone, nefazodone, mirtazapine, agomelatine, and vilazodone; and lowest with the reversible MAOI moclobemide [184; 185]. Compared to spontaneous patient reporting, systematic inquiry increases the rate of identifying sexual side effects by ≥60% [185].

Management of sexual side effects in men includes the use of phosphodiesterase-5 inhibitors such as sildenafil, vardenafil, tadalafil, and avanafil as first-line treatment or switching to bupropion [186]. In women, sexual side effect management considers symptoms, age, and potential hormonal contribution when peri- or post-menopausal.

Increased Suicidality

Several papers documenting an increased risk of suicidal thoughts and behavior with antidepressants, primarily SSRIs, have been published over the past decade. A review of the literature found that antidepressant use, including SSRIs, carried a small short-term risk of inducing suicidal thoughts and suicide attempts in persons younger than 25 years of age, with persons 30 to 40 years of age having a lower risk than those younger than 25 years. This risk should be balanced against the well-known beneficial effects of antidepressants that include reduced suicidal ideation and behavior, particularly in the long term. Clinical decision making should weigh the benefits and potential risks and strive to keep the potential risks of antidepressant treatment to a minimum [187; 188].

Discontinuation Symptoms

Antidepressant discontinuation (more appropriately termed withdrawal) symptoms are described by the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), may be experienced by up to 40% of patients when antidepressants are stopped abruptly, and may occur with any antidepressant [158; 189; 190; 191]. SSRI withdrawal symptoms are far more frequent with paroxetine. Common symptoms include dizziness, nausea, headache, confusion, low energy, weakness, sleep disturbance, flu-like symptoms, restlessness, agitation, anxiety, panic, anger, and irritability. Less common and more severe symptoms include electric-shock sensations, vertigo, paresthesia, intensified suicidal ideation, aggression, derealization, depersonalization, and visual/auditory hallucinations. Gradual tapering is a reasonable strategy but does not prevent the onset of SSRI withdrawal [192]. SSRI withdrawal syndrome is least likely with fluoxetine and vortioxetine [158].

Symptoms usually begin within five days of treatment cessation or occasionally during taper or after missed doses [193; 194]. Symptoms are usually mild and self-limiting but may also be severe and prolonged, particularly following abrupt withdrawal. Some symptoms occur more frequently with specific drugs, such as dizziness and electric shock-like sensations with SSRIs and sweating and headache with TCAs [189; 195]. Risk factors include taking antidepressants longer than eight weeks, development of anxiety symptoms during antidepressant initiation (particularly with SSRIs), use of other medications with CNS activity (e.g., antihypertensives, antihistamines, antipsychotics), and a history of previous discontinuation symptoms [195; 196]. Outpatients who discontinued escitalopram and developed a withdrawal syndrome (56%) had significantly higher mean escitalopram doses and higher plasma concentrations reflecting delayed clearance of escitalopram, than patients without withdrawal. Escitalopram treatment duration, age, and sex were unrelated to withdrawal risk [197].

Symptoms may be severe enough to interfere with daily functioning, and although a four-week taper is usually suggested, some patients may require longer periods, particularly with paroxetine and venlafaxine [198]. Treatment is pragmatic. If symptoms are mild, reassure the patient that this is a common occurrence and that the symptoms will pass in a few days. If symptoms are severe, reintroduce the original antidepressant or a replacement from the same class with a longer half-life, and taper gradually while monitoring for symptoms. Patients should be emphatically informed that the possible or actual emergence of discontinuation symptoms is not a manifestation of addiction to the antidepressant [68]. SSRI withdrawal can also be approached by switching to a course of fluoxetine, such as 10 mg for several weeks, which is slowly tapered and discontinued [22].

Extended-release venlafaxine has the most severe withdrawal syndrome of any antidepressant. In addition to serotonergic withdrawal symptoms, persistent visual images and sensory disturbances are frequently reported. Electrical shock-like sensations in the brain or the sensation of the brain shivering has also been described. This sensory disturbance, often accompanied by dizziness, headache, and disorientation, is distressing to patients and may persist for months after cessation of the drug [199; 200]. Other unexpected symptoms that may emerge include gait difficulties, delirium, suicidal ideation, hypomania, or mania. The usual onset of withdrawal is one to four days post-cessation or with dose reduction [201].

The origin and treatment of these highly distressing sensory symptoms are unknown, but case reports describe positive response to noradrenergic agents. Abrupt cessation of extended-release venlafaxine 37.5 mg led to sensations that "felt like the brain was shaking inside the skull," with anhedonia, anxiety, tinnitus, headache, nausea, and increased noise sensitivity. A trial of atomoxetine (40 mg/day), a norepinephrine transporter inhibitor, led to immediate improvement in "brain shivers" two to three hours from the first dose [199]. Post-cessation electric shock-like sensations and dizziness were greatly reduced by low-dose clonidine (0.05 mg twice-daily). These positive responses suggest an underlying noradrenergic rebound mechanism [200].

Medication Interactions

Most antidepressant drugs have clinically significant drug interactions and it is beyond the scope of this course to discuss all possible interactions. Practitioners are encouraged to consult references such as the Physician's Desk Reference or the American Hospital Formulary Service for information about adverse drug-drug interactions.

Strategies to Manage Side Effects

Research has found that prescribing clinicians consistently underestimate both the frequency of side effects and patient discomfort caused by them, with distress caused by blurred vision and constipation being the most underestimated [202]. The suggested management of many side effects consists of either reducing the dose or discontinuing the medication. However, several focused interventions for specific side effects can be implemented when patients are reluctant to discontinue or switch to another medication, when the side effect is mild-to-moderate in severity, or when there is evidence of treatment response (***Table 3***) [22].

ADDITIONAL CONSIDERATIONS WITH INITIAL THERAPY

Duration of Initial Treatment

Response trajectories are highly variable following antidepressant initiation for MDD. Some patients show robust improvements within one to three weeks, while others have a slower velocity of symptom change. A sizeable subgroup lacks response, and an underidentified subgroup worsens [150; 203].

In predicting substantive response or remission six to eight weeks after treatment initiation, symptomatic improvement by two to three weeks is a modest predictor, but minimal symptomatic improvement by two to three weeks is a far more robust negative predictor of poor or non-response that signals the need to optimize treatment intensity [150; 203; 204; 205].

TREATMENT OF SIDE EFFECTS ASSOCIATED WITH ANTIDEPRESSANT USE	
Side Effect	**Treatment**
Orthostatic hypotension	Fludrocortisone Add salt to diet
Dry mouth	Pilocarpine oral rinse Gum and/or hard candy
Constipation	Hydration Bulk laxatives
Urinary hesitancy	Bethanechol
Visual changes	Pilocarpine eye drops
Sedation	Bedtime dosing Modafinil, armodafinil, methylphenidate
Insomnia	Morning dosing Trazodone or melatonin at bedtime
Myoclonus	Clonazepam
Seizures	Antiepileptic medication
Impaired sexual arousal, erectile dysfunction, orgasm dysfunction	Sildenafil Tadalafil Buspirone Bupropion Flibanserin
Hyperlipidemia	Statin medication
Akathisia	Beta-blocker Benzodiazepines
Diaphoresis	Terazosin Clonidine Benztropine
Weight gain	Exercise Other antidepressant with less weight promotion, if necessary
Source: [22]	*Table 3*

From a clinical perspective, it is unrealistic to expect patients with MDD and minimal treatment response to continue with their antidepressant beyond two to four weeks. Integrating best evidence with pragmatism, intervention is recommended with insufficient outcome (symptom reduction ≤20%) after two to four weeks of treatment [62; 150]. With minimal improvement by two to four weeks, the recommended approach is to increase the dose, if the initial antidepressant is tolerated, or switch to another antidepressant if side effects are problematic [158].

Comparative Discontinuation Rates Due to Side Effects

A meta-analysis of randomized controlled trials involving second-generation antidepressants found that overall discontinuation rates did not differ significantly between SSRIs as a class and bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. The higher discontinuation rate of venlafaxine versus SSRIs due to side effects (11.5% vs. 8.5%) was balanced by lower discontinuation rates due to lack of efficacy (3.5% vs. 4.4%) [122].

Collaboration with Mental Health Professionals

Primary care providers should consider collaborating with behavioral healthcare providers when caring for patients with depression, especially in the following situations [21]:

- Patient request for psychotherapy
- Severe symptoms and impairment in patient
- High suicide risk
- The presence of other psychiatric condition (e.g., personality disorder, history of mania)
- Suspicion or history of substance abuse
- Clinician discomfort with the case
- Medication advice (psychiatrist or other mental health prescriber)
- Patient request for more specialized treatment

Integrate Measurements into Monitoring and Follow-Up

Measurement-based care refers to the systematic use of measurement tools, such as validated rating scales, to monitor the trajectory of disease course and treatment response and support clinical decision-making. Using simple rating scales for measurement-based care of depression can improve outcomes such as symptom remission and adherence [62]. Many of the same instruments previously mentioned in this course can be used for this purpose. Among the most widely used instruments are the Inventory of Depressive Symptoms (IDS), the Quick Inventory of Depressive Symptomatology (QIDS), the HAM-D, the MADRS, the PHQ-9, and the BDI [22].

Routine monitoring of patient outcomes should go beyond assessing depression symptoms by including the ongoing evaluation of functional impairment and quality of life. These outcomes are more important and relevant to patients, and each may vary independently of symptoms. Assessing functionality should include evaluating social and occupational/educational functioning. Quality-of-life assessments offer the opportunity to more broadly evaluate patient well-being and overall health satisfaction [62]. The use of measurement tools should supplement and not replace clinician judgment [206; 207].

HERBAL MEDICATIONS, DIETARY SUPPLEMENTS, AND ALTERNATIVE THERAPIES

Up to 50% of patients with depression use complementary therapies [208]. Herbal medications, dietary supplements, and alternative therapies for depression are appealing to many patients because they are perceived as being natural, helpful, and free of the potentially troubling side effects associated with pharmaceutical antidepressant treatment. Patients ambivalent about taking psychiatric medication are also likely to gravitate to these therapy approaches [209].

All patients should be asked if they are taking over-the-counter dietary supplements or herbal medications, to avoid adverse drug-drug interactions. Because many patients use complementary/alternative therapies, clinicians should have a clear understanding of the most common modalities and potential impact on treatment course and outcomes.

Acupuncture

Acupuncture treatment of depression has shown mixed results, with some randomized controlled trials showing a significant treatment effect and others showing no significant difference from controls. Acupuncture may be an option for those who reject conventional treatments, for patients with milder depression, or for pregnant or nursing women for whom the risks of pharmacotherapy are greater [21].

S-adenosylethionine (SAMe or Sam-E)

S-adenosylethionine (SAMe) is a naturally occurring compound that is present in most parts of the human body and is involved in immune processes and the metabolism of dopamine, serotonin, and melatonin. Several studies have found that compared with placebo, SAMe is efficacious in oral doses of 800–1,600 mg/day, with side effects that were mild and transient. Overall, parenteral and oral formulations of SAMe are comparable to TCAs in efficacy in the treatment of MDD and are better tolerated. SAMe may also have comparable efficacy to TCAs in subgroups such as postpartum women and patients with HIV [22].

Hypericum perforatum (St. John's Wort)

St. John's wort possesses an SSRI-like mechanism, and although considered a first-line antidepressant in many European countries for mild-to-moderate depression, there is no consensus on its efficacy in MDD. Overall, the data suggest that St. John's wort has efficacy comparable to low-dose TCAs in mild-to-moderate depression but is better tolerated by patients. However, St. John's wort interacts with many drugs, including other antidepressants, warfarin, oral contraceptives, and antiretroviral, anticancer, and antirejection drugs. With numerous potential drug interactions, St. John's wort cannot be considered a benign agent, and further studies are needed [175; 210; 211; 212; 213; 214; 215].

Inositol

Myo-inositol is a glucose isomer and an essential component of the phosphatidylinositol second messenger system, which is critically linked to several CNS receptor signaling systems [216; 217; 218; 219]. Randomized controlled trials have found inositol treatment superior in efficacy to placebo in the treatment of major depression, panic disorder, and obsessive-compulsive disorder, and equivalent to fluvoxamine 150 mg/day in panic disorder [216; 220; 221; 222]. The effective daily dose is 12–18 grams, and inositol at 18 g/day is free of side effects other than loose stools and drowsiness [223]. These results need replication in larger trials but are intriguing. A 2010 study demonstrated that patients with severe depression receiving repetitive transcranial magnetic stimulation therapy showed significantly elevated myo-inositol levels in the left prefrontal cortex; greater elevation correlated with more robust clinical improvement [224]. A small meta-analysis published in 2014 suggests that inositol may be particularly beneficial for patients with premenstrual dysphoric disorder [225]. Myo-inositol is available in nutritional supplement stores but is largely unknown as an antidepressant and anxiolytic in the United States.

Folate

The use of folate in non-folate-deficient patients with MDD may be most effective as augmentation to SSRIs such as fluoxetine. Persons receiving fluoxetine and folate may have fewer side effects from the SSRI than those receiving fluoxetine alone [22].

Saffron (*Crocus sativus L.*)

Saffron is a spice that has been used for the treatment of depression in Persian traditional medicine. Its proposed mechanism involves serotonergic, antioxidant, and anti-inflammatory effects [226]. Several well-designed clinical trials have evaluated the efficacy of saffron 30 mg daily over six to eight weeks in mild-to-moderate depression. The results suggest saffron may be more effective than placebo, at least comparable in efficacy to therapeutic-dose imipramine and fluoxetine in reducing depressive symptoms, and without significant side effects. However, this evidence should ideally be replicated in Western populations [227; 228; 229; 230; 231].

Omega-3 Fatty Acids

Evidence suggests omega-3 fatty acids may be beneficial in mood disorders. Treatment efficacy in MDD cannot be determined, but subgroups such as children and pregnant women may show meaningful clinical response. Side effects are minimal [22].

Sleep Deprivation

Sleep deprivation therapy involves staying awake through one night and the following day, without any sleep. Although the proposed antidepressant mechanism is poorly understood, clinical trials have consistently shown that around 60% of depressed persons experience moderate improvement to total remission. However, relapse occurs in 50% to 80% of responders within several days of treatment. Persons with mild depression usually experience a worsening of symptoms [209]. A 2022 systematic review and meta-analysis found no evidence of benefit for sleep deprivation therapy in reducing depressive symptoms [232].

Bright-Light Therapy

Bright-light therapy is effective in patients with MDD with season variation (i.e., seasonal affective disorder) and may also be efficacious as monotherapy treatment of MDD without season variation. The correct intensity of light is essential and should be 3,000 to 10,000 lux-hours of white light, administered at least 30 minutes per day [22]. Results of a systematic review suggest that bright-light therapy at 5,000 lux or greater for periods of 30 minutes or more may be useful as an augmentation to standard antidepressant pharmacotherapy for treatment of MDD [233].

Botulinum Toxin A Injection

Botulinum toxin A injection is emerging as a novel, effective treatment for MDD. It is widely used in aesthetic medicine to treat glabellar frown lines and has been introduced in the treatment of headaches, muscle pain, and tremor. Patient reports of diminished irritable, depressed, and anxious mood following injection led to its evaluation as treatment of MDD. The first trial of botulinum toxin A (29 units in women, 39–40 units in men) in moderate-to-severe chronic MDD found remission in eight of nine subjects after a single injection in the glabellar region [234]. Functional MRI of patients with MDD shows diminished amygdala responses to negative stimuli after injection of botulinum toxin A, confirming that afferent feedback from the corrugator muscle to the amygdala is reversibly severed [235].

In pooled results from three subsequent randomized controlled trials, single-treatment botulinum toxin A led to significantly greater reductions in mean depression scores (47% vs. 16%), response (52% vs. 8%), and remission (42% vs. 8%) rates than placebo. Age, sex, depression severity, and current antidepressant use were not significantly related to response [235]. One small trial found greater response in patients with higher anxious or agitation levels [236]. Symptom reduction is noted around two weeks post-injection and efficacy wears off by three to six months; maintenance injections every three months can be used for relapse prevention. A study from 2021 found that the efficacy of botulinum toxin A was comparable with the antidepressant sertraline for treatment of depression [237]. Use of botulinum toxin A for MDD is currently in phase 3 clinical trials and is off-label [238].

STRATEGIES FOR INADEQUATE RESPONSE TO INITIAL THERAPY

If a patient fails to adequately respond to an initial antidepressant and/or psychotherapy trial, the clinician should consider adjusting the treatment plan, re-evaluating the initial diagnosis, and/or optimizing the prescribed therapy. If the patient remains unresponsive to treatment, referral to a psychiatrist may be indicated.

Optimize Treatment

Optimizing treatment helps to ensure the patient is receiving the most potential benefit from their initial antidepressant. This involves optimizing the dosage and adherence to treatment.

Increase the Dose of the Initial Antidepressant

There is substantial evidence that many patients receive sub-therapeutic doses. When the antidepressant is tolerable but partial or no response is shown by three to four weeks, increase the dose by increments to the highest recommended dose [64]. SSRI dose escalation is supported by a 2016 meta-analysis that found greater response in high-dose ranges, with a plateau at doses greater than 250 mg imipramine-equivalent. This benefit is somewhat offset by decreased high-dose tolerability [239].

EVIDENCE-BASED INTERVENTIONS TO IMPROVE PATIENT ADHERENCE TO ANTIDEPRESSANT MEDICATION	
Intervention	**Overview**
Patient education	Inform patient of the causes and course of depression, and the effects, duration, and side effects of treatment.
Patient-provider empathy/alliance	Establish a good relationship between patient and provider, with an emphasis on communication, consensus, and understanding.
Clinical management strategies	Provide advice regarding a standardized approach to taking medications and compliance, and allow for frequent follow-up visits, especially during initial phases of treatment.
Simplicity of treatment	Minimize the number and doses per day of medication.
Active management of side effects	Inform patient about side effects, monitor their occurrence, provide reassurance, and adjust the treatment if needed.
Behavioral feedback	Help patients incorporate treatment into daily routine (e.g., modify schedule to fit medication routine, behavioral reminders, pill boxes, easy-to-read prescription labels).
Preference for SSRIs	When possible, use SSRIs due to greater tolerability relative to TCAs.
Physician training	Improve skills on caring for patients with depression and patient adherence to treatment.

Source: [242] *Table 4*

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Psychiatric Association recommends optimizing the medication dose as a reasonable first step for patients treated with an antidepressant who have not responded fully to treatment if the side effect burden is tolerable and the upper limit of a medication dose has not been reached.

(https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Last accessed June 18, 2026.)

Strength of Recommendation: II (Recommended with moderate clinical confidence)

Enhance Treatment Adherence

Patient nonadherence can result in nonresponse to the optimal antidepressant regimen, and intolerance of side effects strongly influences therapy nonadherence [240]. Poor adherence is a major problem for patients receiving antidepressant treatment, with discontinuation rates ranging from roughly 30% in clinical trial settings to as high as 60% in clinical practice [241; 242]. In an evaluation of patient adherence to antidepressant medications, 28% had discontinued treatment within the first month and 51.2% had stopped their antidepressant medication by the fourth month [243]. At all timepoints, roughly 64% of patients cited side effects as the reason for stopping their medication.

Compared with usual care, support programs (i.e., a collaborative care model) that educate patients on the value of medication adherence and the potential side effects of antidepressants and provide follow-up to ensure continued compliance have been found to improve the efficacy of depression treatment (***Table 4***) [244; 245]. Other research has shown that patients receiving five specific instructions were significantly more likely to continue their medication through the first month of therapy [64; 243]:

- Take the antidepressant daily.
- Antidepressants must be taken for at least two to four weeks to see a noticeable effect.
- Continue to take the antidepressant even if you feel better.
- Do not stop taking antidepressants without checking with your healthcare provider.

- Follow instructions to contact your healthcare provider when questions arise about antidepressants.

Interventions to improve medication adherence have been found to be effective for up to six months, but the evidence for long-term effectiveness is insufficient and further research is needed [246].

Re-Evaluate the Diagnosis

Most patients with MDD have comorbid conditions that can contribute to disease burden and interfere with treatment response [247]. Especially when undiagnosed, MDD with highly anxious features, comorbid panic disorder, social anxiety disorder, or obsessive-compulsive disorder is strongly predictive of poor medication response, side effect intolerance, treatment discontinuation, and worse overall prognosis. Alcohol or substance use disorder contributes to poor treatment response; in these cases, involve addiction specialists as needed [241]. A behavioral health provider should be involved if a personality disorder is present [248]. Patients with bipolar disorder may require a different treatment approach, and hypomanic, mixed, or manic histories may not be apparent during the initial evaluation [21].

Patients with chronic subtypes of depression (i.e., chronic MDD, double depression, recurrent MDD) may take longer to respond to treatment; clinicians or patients may assume non-response and prematurely discontinue treatment. Different depression subtypes may respond preferentially to various antidepressants [249].

Adjust the Treatment

Options for patients lacking benefit from their initial antidepressant include switching antidepressants, switching to or adding psychotherapy, and adjunctive strategies (i.e., adding a second medication). The decisions to switch or add medications should be individualized and based on clinical factors [158]. Clinicians may consider switching to another antidepressant when [158]:

- It is the first antidepressant trial.
- Side effects are poorly tolerated.
- Minimal or no response (i.e., <25% improvement).
- There is more time to wait for a response (e.g., less severe, less functional impairment).
- Patient prefers switching to another antidepressant.

An adjunctive medication may be added when [158]:

- There have been two or more antidepressant trials.
- The initial antidepressant is well tolerated.
- There is partial response (i.e., >25% improvement).
- There are specific residual symptoms or side effects to the initial antidepressant that can be targeted.
- There is less time to wait for a response (e.g., more severe, more functional impairment).
- Patient prefers to add on another medication.

Switch to Another Antidepressant

Lack of response to one first-line antidepressant does not preclude potential benefits from other antidepressants, but the value of switching between classes or within classes of antidepressants is debatable. Switching to an antidepressant with evidence of superior efficacy is recommended over switching to a lower-efficacy antidepressant based on it being in a different class [158]. Among switching strategies for poor initial SSRI response or tolerance, switching to venlafaxine seems most effective [110].

Combining or Switching Antidepressants and Psychotherapy

Switching from an antidepressant to psychotherapy or vice versa appears useful for non-responders to initial treatment [250]. The addition of CBT or another medication can result in similar rates of improvement, although the addition of medication may result in a more rapid response [251].

Psychotherapy may provide better outcomes on adjustment and functional measures such as mood, suicidal ideation, work, and interests. Medication treatment may be superior on vegetative symptoms such as sleep [252].

Improvement with initial treatment with psychotherapy is typically slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this treatment modality may require 8 to 10 weeks before evaluation [21; 253]. If a patient has received psychotherapy and not responded, evaluate the treatment and consider another type.

Augmentation

Patients with MDD often prefer augmentation (add-on) to switching if partial improvement is achieved with the initial agent [254]. Standard antidepressants are frequently used as add-on therapy to enhance efficacy. For example, combining a TCA and an SSRI may be helpful for some patients, but the TCA dose should be adjusted because SSRIs may increase TCA levels [255; 256]. Combining an SSRI, SNRI, or TCA with a presynaptic a2-autoreceptor antagonist (e.g., mirtazapine, trazodone) has shown significantly greater benefit than other combinations, with dosage differences accounting for about 50% of the total difference in treatment effect. Tolerability, as measured in patient dropout, was lower than expected with this combination [257].

Adverse effects are higher in combination pharmacotherapy, and combining antidepressants at treatment initiation is not recommended unless the MDD is characterized as severe (i.e., PHQ-0 >20); chronic (duration longer than two years); and recurrent (three or more episodes) [64]. In patients lacking response to their initial or switched standard antidepressant, evidence indicates that standard monoamine antidepressants are not sufficient for many patients and other mechanistic targets are needed [150].

Aripiprazole has been found superior to switching antidepressants in patients with current depressive episodes, despite adequate antidepressant dosage, and in patients with antidepressant non-response [258]. Brexpiprazole is another atypical antipsychotic effective as add-on therapy; aripiprazole and brexpiprazole are approved by the FDA as augmentation therapies in MDD [64; 150; 192]. Although well tolerated, brexpiprazole does not appear to offer a statistically significant benefit over placebo as an adjunctive treatment [259].

The evidence base for lithium and triiodothyronine shows efficacy, but mainly involves studies that combined these agents with TCAs or MAOIs [150]. Methylphenidate has mostly shown mixed results in reducing depressive symptoms [260; 261].

Modafinil has not shown consistent efficacy in core MDD symptoms, but it has demonstrated improvements in symptoms/dimensions of psychopathology highly relevant to patient function, including fatigue, apathy, anhedonia, amotivation, and cognitive impairment [262]. Adverse effects have not differed from placebo [159; 263].

Lisdexamfetamine, a dextroamphetamine prodrug, showed some evidence of efficacy as an adjunctive agent for partial SSRI responders in two placebo-controlled randomized controlled trials [182; 264]. Pramipexole is a dopamine receptor agonist and a standard therapeutic in Parkinson disease. Preliminary evidence shows some benefit in patients with MDD lacking response to multiple antidepressant regimens [265; 266].

The optimal duration of add-on therapy is not known, but it seems prudent that patients who are tolerating treatment and achieving therapeutic objectives should continue for at least 6 to 12 months with ongoing reassessment, with indefinite continuation for many [150].

TREATMENT-RESISTANT DEPRESSION

Most definitions of treatment response compare changes in depression rating scale scores between pre-treatment and follow-up. Standardized rating scales such as the MADRS and HAM-D are widely used to quantify treatment response [249]. As discussed, the definition of antidepressant response falls into four categories [21; 111]:

- Remission: The absence of depressive symptoms or minimal symptoms (HAM-D score ≤7)
- Response: A 50% or greater reduction in symptoms
- Partial response: A 25% to 50% reduction in symptoms
- Nonresponse: The absence of meaningful response (symptom reduction ≤25%)

Standard antidepressants fail to produce adequate response in 30% to 50% and remission in up to 70% of patients with MDD [267; 268; 269]. Partial response, instead of full remission, leaves patients with impairing residual symptoms and high risk of relapse. Each relapse increases symptom severity, decreases treatment response, and heightens risk of treatment-resistant MDD [270].

Treatment-resistant depression is a problem increasingly encountered by primary care and mental health providers. Contributors to treatment-resistant depression include illness severity, medical and psychiatric comorbidity, and the limitations of FDA-approved drug options. The definition of treatment resistance lacks consensus, but the most common definition is inadequate response to two or more antidepressants. This does not consider adjunctive strategies or distinguish patients with partial versus non-response [158; 180].

In addition to augmentation strategies discussed, a diverse and growing range of interventions are available as options for treatment-resistant depression. Most engage novel therapeutic targets.

OPTIONS FOR TREATMENT-RESISTANT DEPRESSION

Bright-Light Therapy

As mentioned, use of bright-light therapy for treatment of major depression with a seasonal specifier (seasonal affective disorder) is well established [271; 272]. There is also evidence supporting its use for additional types of depressive symptom patterns, including non-seasonal depression, milder variations of seasonal depressive patterns, and depression in pregnant and postpartum women [273; 274; 275]. Bright-light therapy may quicken and enhance the effects of antidepressants [276]. The interaction between light intensity and duration of exposure requires two hours daily with 2,500 lux, one hour with 5,000 lux, and 30 minutes daily with 10,000 lux for efficacy [277]. Light therapy must also use equipment that eliminates ultraviolet frequencies.

Neurostimulation Therapies

The limitations of standard antidepressants, frequent treatment resistance, and the paradigm shift in psychiatry away from specific neurotransmitter focus and toward an integrative neural network perspective has prompted the development of novel depression treatment approaches, such as neurostimulation therapy. Neurostimulation therapies include a range of techniques that deliver electrical or magnetic stimulation to specific brain region targets for the treatment of refractory psychiatric and pain conditions. Neurostimulation efficacy in neurologic disorders led to their introduction in psychiatry. In addition to ECT, several others are now FDA-approved for use in MDD and related disorders.

The dorsolateral prefrontal cortex is a common brain stimulation target in patients with MDD. Its normal regulatory function of control over stress and emotion reactivity is thought to be hypoactive in MDD. The dorsolateral prefrontal cortex and rostral anterior cingulate cortex areas are closely inter-connected; decreased activity in these frontal areas accounts for apathy, psychomotor slowness, and impaired executive functioning common in patients with MDD [278; 279; 280].

Electroconvulsive Therapy

ECT remains established as a potent and rapidly acting treatment for severe or refractory MDD and is considered unrivaled among standard options for rapidly inducing antidepressant effects. ECT is effective as acute treatment, but multiple treatments are required and many who respond experience symptoms again within six months [281]. ECT generates electrical stimuli for seizure induction through electrodes applied to the scalp, with the patient under general anesthesia and pre-medicated with a muscle relaxant. Clinical outcomes are highly influenced by electrode placements, electrical intensity, and pulse width [282]. Seizure-induced changes in neurotransmitter activity, neuroplasticity, and functional connectivity account for its effects. ECT also increases brain-derived neurotrophic factor, which may promote neuroplasticity and contribute to the antidepressant effect [282; 283].

As first-line treatment, ECT is used for severe melancholic, catatonic, psychotic, or refractory depression and for patients who refuse to eat or drink, have very high suicide risk or severe distress, pregnant women with severe depression, or who have a previous positive ECT response [64; 281; 284]. A large study reported 95% remission in study completers [285]. Full ECT response requires at least four to six sessions delivered two to three times per week. Twice weekly ECT requires longer treatment duration, but more than three treatments per week is not recommended due to the greater cognitive side effect risk [282]. Relapse rates are greatest in the first six months post-ECT (37.7%). Even patients with maintenance ECT show high relapse rates at one year (51.1%) [286]. Severity of treatment resistance predicts poor ECT response [287; 288].

Adverse Effects

Headaches (45%), muscle soreness (20%), and nausea (1% to 25%) during ECT are transient and treated symptomatically; 7% of patients with MDD switch into a manic or mixed state [282]. Cognitive impairment includes transient post-ECT disorientation, retrograde amnesia (i.e., difficulty recalling information learned pre-ECT), and anterograde amnesia (i.e., difficulty retaining information learned post-ECT). Mild, short-term memory and cognitive impairments are common during, and just after, ECT [284]. Within two to four weeks, impaired anterograde memory usually returns to normal or may improve from pre-ECT levels [289]. Retrograde impairment can persist for prolonged periods [290]. Most distressing to some patients is loss of autobiographic memory recall, infrequently reported to persist beyond six months [284]. ECT lacks absolute contraindication, but increased safety risk is associated with space-occupying cerebral lesion, increased intracranial pressure, recent cerebral hemorrhage, or aneurysm [282; 283].

Vagus Nerve Stimulation

Vagus nerve stimulation uses an implantable device to provide intermittent stimulation to the left vagus nerve (80% afferent to the CNS) [21]. It received FDA approval for treatment-resistant depression in 2005 due to the lack of approved drug treatments and concerns over the long-term efficacy and safety of ECT [291].

Controlled studies with follow-up six months or longer have found significant improvements in depressive symptoms that were often sustained over time, with relapse rates relatively low [292]. Long-term vagus nerve stimulation can lead to significant side effects, including decreases in airway flow and respiratory effort and laryngopharyngeal dysfunction [293]. Given the profound negative impact of treatment-resistant depression and lack of durable response in some patients, vagus nerve stimulation may be a useful option [294]. In a 2017 trial, patients with treatment-resistant MDD and four or more failed depression treatments (including ECT) received vagus nerve stimulation or treatment as usual and were followed five years. Response was a ≥50% decrease in MADRS score at any follow-up visit. Subjects who received vagus nerve stimulation (compared with usual treatment) had more severe treatment-resistant depression on several dimensions [295]. Vagus nerve stimulation led to greater five-year cumulative response (67.6%) and remission (43.3%) rates compared with usual treatment (40.9% and 25.7%, respectively). However, vagus nerve stimulation response often required 12 or more months to appear [295]. Guidelines recommend against the use of vagus nerve stimulation outside a research setting [64].

Deep Brain Stimulation

With deep brain stimulation, an electrode is surgically implanted to stimulate the subgenual cingulate gyrus with high-frequency impulses to reduce depressive symptoms [21]. Deep brain stimulation is invasive and carries the risk of infection, hemorrhage, and other surgical complications. Stimulation-induced adverse effects such as facial contractions, facial paresthesias, olfactory phenomena, anxiety, and mood fluctuations have been reported, particularly at higher levels of stimulation [296].

Most clinical improvement shows delayed onset; one trial in patients with treatment-resistant depression reported remission rates of 27%, 24%, and 37% at three-month, six-month, and two-year follow-up, respectively [297]. Deep brain stimulation can increase the risk of suicide ideation, attempts, and death, strongly indicating that patients should be pre-screened for suicide risk and monitored closely for suicidal behavior pre- and postoperatively [298]. Deep brain stimulation is investigational for treatment-resistant depression and is reserved for use in patients with severe refractory psychiatric, neurologic, or chronic pain conditions [282; 296].

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation delivers high-intensity magnetic pulses to the cortex through a stimulating coil placed to the forehead [299; 300]. It is a first-line MDD treatment in patients with one or more failed antidepressant trial [282]. Efficacy in treatment-resistant depression was established using stringent criteria; analysis of 23 trials found significantly greater efficacy and effect size for repetitive transcranial magnetic stimulation over sham [301]. In randomized clinical trials, 20 to 30 sessions over four or more weeks achieved 40% to 55% response and 25% to 35% remission rates [302].

The most frequent side effects are transient scalp pain (40%) and headache (30%). Both diminish with repeated treatment and respond to over-the-counter analgesics. The cognitive safety profile is benign. Seizures are the most serious side effect, but fewer than 25 cases have been reported worldwide [282; 303]. Repetitive transcranial magnetic stimulation is contraindicated in patients with any metal or metallic hardware in the head (except the mouth), with a history of seizures, and who take medications that lower seizure threshold [282; 304].

Transcranial Direct-Current Stimulation

A sham-controlled trial randomized patients with MDD to escitalopram (20 mg/day) or prefrontal transcranial direct-current stimulation for 10 weeks. With mean decrease in HAM-D score from baseline, both treatment groups were superior to placebo, but transcranial direct-current stimulation was inferior to escitalopram. New-onset manic switch during transcranial direct-current stimulation therapy is a concerning adverse event; however, the number of reported cases is low [283; 305; 306].

Magnetic Seizure Therapy

Magnetic seizure therapy uses focused brain stimulation (generally of the right frontal area) to induce a focal seizure. It intends to produce the efficacy of ECT without the cognitive side effects by sparing the hippocampus from seizure activity [21]. A meta-analysis of 1,092 patients with treatment-resistant depression found response and remission rates for active vs. sham magnetic seizure therapy of 25% and 17%, versus 9% and 6%, respectively [307]. A 2016 meta-analysis found that while magnetic seizure therapy had a small short-term effect in improving depression compared with sham, follow-up studies did not demonstrate that the small effect would continue for longer periods [308]. A study of 23 patients with treatment-resistant depression found that 44.4% of the group experienced resolution of suicidal ideation following magnetic seizure therapy [309]. Magnetic seizure therapy add-on to SSRI treatment in treatment-resistant depression improves outcome, but more data is needed before it can be considered a first-line therapy for treatment-resistant depression [307; 310].

Pharmacotherapies

Ketamine

Ketamine is an *N*-methyl-D-aspartate receptor (NMDA-R) antagonist that was approved for use as an anesthetic in 1970. Demonstration that a single IV dose in patients with treatment-resistant depression reliably produced rapid, robust antidepressant effects for one week was a breakthrough discovery for research and a turning point for patients for whom all other treatment approaches had failed [311]. The short-term efficacy of ketamine treatment of refractory MDD and bipolar depression is now established; over a dozen placebo-controlled trials have shown that patients with refractory MDD or bipolar depression have significantly greater response, remission, and depressive symptom reduction to single-dose IV ketamine than placebo from 40 minutes through days 10 to 12 post-treatment [312; 313]. The approach has become standardized, using a sub-anesthetic dose: 0.5 mg/kg IV over a 40-minute infusion. In a 2015 analysis, ketamine was designated as one of two psychiatric treatments that had the highest potential impact on patient outcomes. This designation was based on the serious unmet need for fast-acting, well-tolerated antidepressants with efficacy in refractory MDD and bipolar depression [47].

Substantial interest and optimism among patients, families, patient advocacy groups, and clinicians has been generated by clinical reports of unique antidepressant effects with ketamine and frequent media coverage of potential ketamine treatment benefits. Demand for clinical access to ketamine treatment is rapidly escalating, and a growing number of clinics and practitioners are now offering various forms of ketamine treatment for mood and anxiety disorders throughout the United States [314]. However, many in the field suggest greater caution, and concerns that enthusiasm and desperation of patients and families may be leading to ketamine used in ways that are not yet supported by existing evidence. Others note the lack of large-scale or long-term studies of ketamine treatment in refractory MDD [314]. Use of IV ketamine for treatment-resistant depression is off-label, whereas an intranasal formulation (esketamine) is FDA-approved for treatment-resistant depression as monotherapy or in conjunction with an oral antidepressant, and for MDD with suicidality, when used in conjunction with an oral antidepressant [64; 175]. A systematic review and meta-analysis of five randomized controlled trials found that twice-weekly dosing of esketamine as augmentation to ongoing oral antidepressant use compared with placebo improved depressive symptoms and remission in patients with MDD at up to 28 days follow-up [315].

Rapastinel

Rapastinel is an investigational NMDA-R partial agonist with robust cognitive enhancement and rapid, long-lasting antidepressant effects. This drug comes as a pre-filled IV syringe, administered in less than one minute. After one injection, therapeutic effects appear within two hours and last up to seven days. Rapastinel is well-tolerated, and antidepressant effects last up to 10 weeks with repeat dosing. The drug has no psychotomimetic effects, may be neuroprotective, and may enhance aspects of learning and memory. The long-lasting therapeutic benefits are explained by significant effects on metaplasticity processes in the medial prefrontal cortex and hippocampus [316; 317].

Buprenorphine

Opioids were widely used as depression treatment from roughly 1850 until 1956, when they were replaced by standard antidepressants. Their antidepressant potential has rarely been studied in the past 60 years, but this seems to be changing. The synthetic opioid buprenorphine is a partial mu opioid receptor agonist and kappa opioid receptor antagonist. It is safer in overdose with substantially less euphoria than traditional opioid analgesics such as morphine and oxycodone. A small, open-label study in 1995 hinted that buprenorphine might have benefit in refractory depression [318].

Buprenorphine/samidorphan combination (BUP/SAM) is an opioid system modulator being investigated as an adjunctive treatment for MDD. It is a fixed-dose combination of buprenorphine and samidorphan (a mu opioid receptor agonist). Samidorphan was added to address the abuse and dependence potential of buprenorphine [319]. A 2019 long-term open-label extension study examined the efficacy and adverse effects of adjunctive BUP/SAM [320]. All patients had confirmed MDD and a current MDE lasting 2 to 24 months. Patients were treated with an established antidepressant therapy for a minimum of 8 weeks before receiving sublingual BUP/SAM (2 mg/2 mg) for up to 52 weeks. Safety was assessed via reported adverse events, the Columbia-Suicide Severity Rating Scale, and the Clinical Opiate Withdrawal Scale. Evaluation of efficacy was achieved using MADRS. Of 1,485 patients, 50% completed the study; 11% withdrew due to adverse events (e.g., nausea, headache, constipation, dizziness, somnolence). Drug withdrawal adverse events were infrequent, and euphoria-related adverse events were uncommon. There was no evidence of increased suicidal ideation or behavior. Improvements in MADRS scores were maintained until the end of the study, suggesting durability of antidepressant effect. BUP/SAM was generally well tolerated, with a low risk of abuse [320].

Celecoxib

The cyclooxygenase-2 inhibitor celecoxib has demonstrated significant reductions in depressive symptoms compared to placebo as an SSRI add-on in MDD treatment. The decrease in depressive symptoms begins after the first week. However, celecoxib and all other nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with risk of serious cardiovascular events [321].

Statins

Two studies compared statins to placebo as add-on therapy to fluoxetine in the treatment of MDD. In one trial, 30 mg/day lovastatin for six weeks improved antidepressant effects compared to placebo [322]. The other trial found simvastatin 20 mg/day for six weeks significantly decreased depressive symptoms, but remission did not differ from placebo [323].

Statins have relatively few side effects; the most dangerous—rhabdomyolysis—is a very rare event. Statins are primarily used in prevention of cardiovascular events but may have a more favorable benefit/risk balance than other drugs, such as NSAIDs, considering the high cardiovascular comorbidity in persons with depression [324]. Other less common side effects include myopathy, hepatotoxicity, peripheral neuropathy, impaired myocardial contractility, and autoimmune dysfunction.

Silexan

Silexan is a substance derived from Lavandula angustifolia flowers that increases extracellular serotonin levels. Approved in Germany for the treatment of restlessness related to anxious mood, its antidepressant effects were tested in a randomized controlled trial of 318 patients with mixed anxiety and depressive disorder. Silexan (vs. placebo) significantly reduced MADRS and Hamilton Rating Scale for Anxiety (HAM-A) scores. Antidepressant effects were noted after 2 weeks, became statistically significant at 4 weeks, and remained significant through the 10-week trial [123; 321].

Psilocybin

Psilocybin is a classical psychedelic and naturally occurring alkaloid found in the *Psilocybe* genus of mushrooms [325]. Its potential efficacy in the treatment of depression is a recent focus of research interest.

The feasibility, safety, and efficacy of open-label psilocybin were studied in 12 patients with treatment-resistant depression (2 to 13 failed antidepressant trials). All patients received 10-mg (low-dose) oral psilocybin, 25-mg (high-dose) psilocybin one week later, and psychologic support during all sessions. Relative to baseline, depressive symptoms were markedly reduced one week and three months after high-dose treatment. Remission was achieved by 67% at one week and 42% at three months. Marked and sustained improvements in anxiety and anhedonia were also noted. Psilocybin was well tolerated by all patients, without serious or unexpected adverse events [325]. A 2026 study of 19 patients with treatment-resistant depression who underwent one to four sessions of orally administered synthetic psilocybin found similar, though slightly smaller, reductions in baseline depression, measured as changes in BDI-II and MADRS screening scores [505].

Two psilocybin treatment studies in patients with life-threatening cancer and high levels of depressive and anxious distress were published in 2016. One trial compared low-dose psilocybin (0.3 mg/kg) with niacin placebo, and the other trial compared low-dose (1 or 3 mg/70 kg) and high-dose (22 or 30 mg/70 kg) psilocybin [326; 327]. Patients in all sessions were accompanied by trained therapy support. Both studies reported significant improvements in depression and anxiety scores, measures of spiritual well-being, emotional distress related to the cancer, and quality of life. Immediate post-treatment gains were sustained for six-month study durations by 60% to 80% of subjects. These studies confirmed psilocybin could be given safely without significant adverse effects in a controlled environment with trained therapists [326; 327].

PERINATAL DEPRESSION

Approximately 5% to 14% of women experience significant mood or anxiety symptoms during pregnancy, and the goal of perinatal treatment is to minimize the risks of both depression and its treatment to the mother and child [328; 329]. Misperception about treatment risk can result in the termination of otherwise wanted pregnancies or avoidance of needed pharmacotherapy. By informing patients of both the nature of medication risks and the risks of untreated illness, providers can help patients reach their own educated decisions.

For depressed pregnant women, both continuous SSRI exposure and continuous untreated depression are associated with preterm birth rates in excess of 20% [330]. The potential impact of untreated maternal depression on pregnancy outcome and infant health include preterm birth and low birth weight, birth defects, developmental delay and cognitive impairment, behavioral and emotional maladjustment, and poor maternal health behaviors such as smoking and alcohol and substance use, which secondarily affect birth outcome [331].

FDA RATINGS OF ANTIDEPRESSANT PREGNANCY RISK	
Rating	**Definition and Examples**
A	No currently available antidepressant medications are rated A, which would indicate a failure to demonstrate risk to the fetus in well-controlled studies of pregnant women.
B	Maprotiline—no evidence of risk in humans, and either animal findings show risk but human findings do not, or animal findings are negative if no adequate human studies have been performed.
C	Amitriptyline, amoxapine, bupropion, protriptyline, sertraline, trazodone, trimipramine, and venlafaxine—risk cannot be ruled out, and although human studies are lacking and animal studies are either positive for fetal risk or are lacking, potential benefits may justify the potential risks.
D	Imipramine, nortriptyline, and paroxetine—positive evidence of risk. Investigational or postmarketing data show risk to the fetus. The potential benefits may outweigh the potential risks, and if needed in a life-threatening situation or a serious disease, the drug may be acceptable if safer drugs cannot be used or are ineffective.
X	No currently used antidepressant medications are rated X, which would indicate that use is contraindicated in pregnancy due to animal or human studies that conclude that fetal risk clearly outweighs potential benefits.
Source: [21]	*Table 5*

MILD-TO-MODERATE DEPRESSION

Several non-drug therapies effective in mild-to-moderate depression are available for pregnant and breastfeeding women, including interpersonal psychotherapy, bright-light therapy, and CBT [332; 333; 334]. Interpersonal therapy is efficacious in postpartum depression and can improve functioning for six months postpartum [334]. While these interventions are more efficacious than routine care for postpartum depression, there is little indication of superiority for any one intervention [334]. Other nonpharmacologic treatments that may be effective include acupuncture, progressive relaxation, music therapy, sleep deprivation, and exercise [331]. Empirical support for nutritional or supplemental omega-3 fatty acids is lacking, although they pose little to no risk of adverse effects [335]. Progesterone is ineffective in postpartum depression and may intensify depressive symptoms in some patients [331].

SEVERE DEPRESSION

In many circumstances, the risks of untreated illness may outweigh the potential negative effects of certain antidepressant medications. Partial SSRI treatment during pregnancy to reduce the risk of preterm birth is not recommended, as inadequate dosing does not successfully treat the depression. When possible, medication choice should be based on what has worked previously and the risk/benefit of continuing the current medication during pregnancy and/or postpartum. Optimal dosing and safety are best ensured by consultation with a health professional with perinatal expertise.

PHARMACOLOGY AND PERINATAL DEPRESSION

The largest amount of reproductive safety information is available for TCAs and SSRIs (***Table 5***). Available pregnancy data have found no evidence that fluoxetine, sertraline, fluvoxamine, venlafaxine, or bupropion are associated with an increased risk of major congenital malformations. In 2006, the FDA warned that paroxetine was associated with increased risk for cardiovascular malformations compared to other antidepressants. Therefore, women of childbearing age taking paroxetine should be advised of the potential risk, and other treatment options, including another SSRI, may be preferred [175; 336].

The use of SSRIs before the 20th week of gestation has not been associated with persistent pulmonary hypertension of the newborn (PPHN), but use of SSRIs in late pregnancy has shown a small but significantly increased risk of PPHN [337; 338].

Several case reports document a perinatal syndrome in infants (e.g., jitteriness, irritability, bowel obstruction, urinary retention) with maternal use of TCAs and most of the SSRIs, although it is unclear whether the neonates were exhibiting symptoms of SSRI toxicity or SSRI withdrawal at birth. Also, they may have been more irritable and difficult to settle due to maternal depression, anxiety, and exposure to psychological stressors [328; 339; 340; 341; 342]. There is a lack of evidence suggesting that reducing or discontinuing antidepressants in late pregnancy will reduce adverse neonatal effects [343].

Women with a history of depression who are planning to become pregnant should carefully consider the choice and timing of an antidepressant [340]. Although SSRIs taken during pregnancy may be associated with adverse neonatal effects that are mostly mild and short-lived, women with a history of recurrent or severe depression who discontinue antidepressants during pregnancy increase the risk of potentially adverse outcomes for both the mother and fetus/infant. The minimum effective antidepressant dose to achieve and maintain remission should be used throughout pregnancy in women who continue their medication, and these patients should be monitored on an ongoing basis [339]. Women who discontinue medication relapse significantly more frequently over the course of their pregnancy compared with women who maintain their medication [344]. The decision to continue treatment during the pregnancy should balance the risks and benefits to the mother and child and should be made on a case-by-case basis [21].

LACTATION

The Academy of Breastfeeding Medicine Protocol Committee suggests that TCAs and SSRIs are relatively safe, but they should only be used when clearly needed. Assessments weighing the potential benefits with the potential risks to the nursing infant should be performed in all cases [345]. Also, the mother-infant pair should be monitored for the emergence of adverse effects or complications [345; 346]. Regarding the use of specific medications during lactation, several observations and recommendations have been made [21; 347; 348]. Sertraline, paroxetine, nortriptyline, and imipramine are the most evidence-based medications for use during breastfeeding; nortriptyline, paroxetine, and sertraline may be preferred choices in breastfeeding women. Use of imipramine during breastfeeding is not recommended by the manufacturer [175]. The lack of adverse effects among infants exposed to fluoxetine justifies its use, especially if prescribed during the pregnancy or if there is a preferential response history. However, its use during breastfeeding is not recommended by the manufacturer [175]. The TCA doxepin should be avoided due to a case report of infant respiratory distress [175]. Data on citalopram, fluvoxamine, bupropion, and venlafaxine are more limited and their use cannot be recommended during breastfeeding [175]. One study evaluating the potential consequences of TCA exposure through breast milk followed exposed children through preschool age and found that exposed children were developmentally similar to non-exposed children. No similar studies have been performed with SSRIs [21].

SUICIDE

For the past 50 years, suicide prevention research has focused on identifying demographic and clinical factors that reliably predict suicide risk. Examining population-level data, researchers found clinical and demographic factors that correlated with suicidality [349]. These variables, including depression, most psychiatric disorders, trait impulsivity, family history of suicide, previous suicide attempts, and current suicidal ideation, became established as suicide risk factors [350; 351]. Suicide risk assessment intends to reduce clinician uncertainty of short-term patient risk of suicide so patients at imminent risk can receive rapid intervention [352; 353]. Decades-old convention holds that assessing suicide risk should culminate in a probability judgment of "low," "moderate," or "high" risk level [349]. Obtaining larger amounts of patient information was believed to be the best means to identify risk factors and reduce uncertainty [353; 354].

However, there is evidence that challenges these foundational assumptions of suicide, including risk factors and risk stratification, long-standing organizing principles of clinical suicide prevention. A 1983 study first identified the limitations of risk factors in suicide prediction, finding that 96.3% of high-risk suicide predictions were false positives and more than 50% of suicides occurred in low-risk patients (false negatives) [355]. Subsequent studies confirmed these results, demonstrating that the clinical reliance on traditional suicide risk assessment, risk factors, and scales were largely overstated [356; 357; 358; 359; 360; 361; 362; 363].

Traditional suicide risk factors are nonspecific, common, non-modifiable, and to varying degrees represent underlying vulnerabilities. These risk factors demonstrably predict lifetime and 12-month suicide ideation, but fail to predict suicide completion, suicide, or movement from ideation to suicide behavior [352]. Many patients have elevated risk profiles, but their lifetime odds of suicide are remote. No study using population-based risk factors or combinations, rating scales, or assessment instruments has successfully predicted suicide in individual patients [350; 351; 364; 365; 366]. The failure to improve suicide prevention and the limited benefit of suicidality interventions suggest inadequate understanding of the mechanisms leading to suicidal behavior [367].

Acute suicide risk is now thought to result from recent psychosocial stressors superimposed on non-modifiable (traditional) risk factors, with psychosocial stressors the precipitants or "triggering events" to suicidal behaviors [364; 368]. Warning signs, or the acute patient response to precipitants, are considered more useful to assess than risk factors [368]. The strongest suicide risk factor—previous suicide attempts—is a static, non-acute factor with low predictive power [369]. While nearly half of suicides made previous attempts, only 5% to 15% of attempters ultimately die by suicide [370; 371]. This seems a robust predictor, but with distribution of risk across the lifespan, even this risk factor does little to inform of acute patient risk level in any given contact [369].

EPIDEMIOLOGY

Suicide rates declined 24% between 1977 and 2000, but then increased 28% between 2000 and 2015. From 1999 to 2015, approximately 600,000 Americans died by suicide [372; 373]. In 2024 alone, 48,824 Americans died of suicide, an average of 133 suicides every day, or one person every 10.8 minutes. Among persons younger than 15 years of age, one suicide occurs every 1.4 hours [374]. Suicide is the 10th leading cause of death in the United States, and the second leading cause for youth 15 to 34 years of age. The annual cost of suicide in the United States is estimated to be $500 billion in medical costs, lost work, the impact of lives cut short, and quality of life costs [72].

White boys and men accounted for 68.6% of all suicides in the United States in 2024; the suicide rate in this population is two times greater than that for non-White boys/men [374]. White girls and women (8,233 suicides in 2024) also have markedly higher suicide rates than their non-White counterparts [374].

In 2024, suicide rates by race/ethnicity were highest in White Americans, followed by, American Indians/Alaska Natives, Native Hawaiian/Pacific Islander, multiracial, Black Americans, Hispanic Americans, and Asian Americans [373]. Overall, adult suicide rates were highest in persons 75 years of age or older and lowest in young adults 15 to 24 years of age, despite suicide being the second leading cause of death in this age group [373]. The NSDUH found few racial and ethnic differences for suicidality [15].

Suicide rates in urban and rural areas diverged during 1999–2015, especially after 2008. This could reflect more prevalent social isolation, financial hardship, access to lethal means (guns), and limited access to mental health care [372].

SUICIDALITY IN ADULTS IN THE UNITED STATES, 2024			
Demographic Group	**Past-Year Suicidal Thoughts**	**Past-Year Suicide Plans**	**Past-Year Suicide Attempts**
All adults	14.3 million (5.5%)	4.6 million (1.8%)	2.2 million (0.8%)
18 to 25 years of age	12.6%	4.2%	2.0%
26 to 49 years of age	6.1%	1.6%	0.8%
50 years of age and older	2.9%	1.1%	0.6%
Males	5.5%	1.8%	0.8%
Females	5.5%	1.7%	0.9%
Past-year use of alcohol or illicit drugs	5.7%	1.7%	0.8%
Past-year use of any illicit drug	10.2%	3.5%	1.6%
Methamphetamine use	19.2%	7.6%	5.3%
Tranquilizer or sedative misuse	15.2%	6.5%	3.1%
Cocaine use	13.7%	5.5%	2.6%
Cannabis use	10.3%	3.4%	1.6%
Heroin use	22.5%	8.3%	4.2%
Past-year substance use disorder	12.0%	4.3%	2.0%
Past-year major depressive episode	29.0%	10.2%	3.8%
Treated for suicide attempt(s)			
Population	**Any Medical Attention**		**Hospitalization**
All adults	1,339,000 (60.8%)		989,000 (44.9%)
18 to 25 years of age	334,000 (41.0%)		249,000 (36.5%)
26 to 49 years of age	527,000 (64.5%)		379,000 (46.3%)
50 years of age and older	Not available		Not available

Source: [15] *Table 6*

Aside from measures of suicide-related deaths, various levels of suicidality among adults have been studied, with suicidal thoughts, plans, and attempts quantified (***Table 6***). In the general population, there are 60 attempts for every suicide. Among adults with past-year suicidal ideation, around 1 in 4 plan suicide and 1 in 7 attempt suicide. For each male attempt are three female attempts, and there are 3.96 male suicides for each female suicide [374].

PATHOPHYSIOLOGY OF SUICIDAL BEHAVIOR

Suicidality is a distinct, multidimensional clinical condition now thought to result from interactions among biologic, social, and psychologic vulnerability factors, proximal biopsychosocial events acting as precipitants, and epigenetic factors [350; 351; 376]. The pathophysiology of suicide is distinct from comorbid psychiatric diagnoses. Previous research identified underlying processes in suicidal ideation, but assumptions that ideation predicted suicide attempts is now disproven, with efforts focused on identifying the underlying pathways to suicide.

To advance this research, two empirically confirmed models of suicide have been developed. The stress-diathesis model of suicidal behavior describes long-term vulnerability to suicide, activated by psychosocial or psychiatric crises [376]. The interpersonal theory of suicide proposes desire and capability as the principal factors contributing to suicidal behavior. Suicidal desire is explained by high levels of burdensomeness (i.e., a belief one is an unwanted burden to family/peers) and thwarted belongingness (i.e., social alienation and loneliness). Capability of suicide reflects the sum of noxious stimuli, traumatic events, and experiences of death and pain [377].

Some suicide neurobiology has also been established, such as associations between suicide and gene variations in the HPA axis, serotonin systems, noradrenergic systems, and polyamines that promote functional alterations. In the absence of gene variations, gene expression can become altered by exposure to extreme or chronic stress, becoming both cause and effect of neurobiologic response [376; 378].

Abnormal function in several neurobiologic systems is associated with suicidal behavior, including the HPA axis, serotonergic system, and noradrenergic system. Dysfunction of these systems is associated with impaired regulation of anxiety, impulsivity, and aggression, which may result from genetic variation and environmental stressors (and their interaction) [379; 380]. This may lead to dysfunctional information processing, eventually contributing to increased capability of suicide [378; 381]. Immune system dysregulation is also believed to contribute to suicidality, but the role of inflammatory conditions has not been clearly delineated [382].

SUICIDE AND SPECIAL POPULATIONS

Youth

Before 18 years of age, 12.1% of youth report suicide ideation and 4.1% make at least one attempt [383]. In 2023, 481 children between the ages 10 and 14 years died by suicide, a rate of 2.3 for every 100,000 children [384]. Between 2008 and 2015, encounters for suicide ideation or attempt at children's hospitals nearly doubled [385]. The presence of acne is associated with social and psychologic problems and twice the rate of suicidal ideation [386].

College Students

Suicide is the second most common cause of death among college students, with an estimated 1,000 students taking their lives on college campuses each year. More than 50% of college students report having had suicidal thoughts, and another 10% report a serious suicide attempt. An estimated 80% to 90% of college students who died by suicide were not receiving help from college counseling centers [387]. A study published in 2019 from the American College Health Association/National College Health Assessment survey assessed mental health diagnoses and suicidality from more than 67,000 undergraduate students across 108 institutions [388]. According to the results, one in five students have had thoughts of suicide, with 9% making a suicide attempt and 20% reporting self-injury [388]. Students leaving home for college face unique challenges that may increase suicide risk in vulnerable students, including separation from support systems and social networks, academic stress, pressure to succeed, feelings of isolation, poor coping skills, and mental health stigma.

ADVERSE EXPERIENCES AND SUICIDALITY AMONG HETEROSEXUAL AND SEXUAL MINORITY HIGH-SCHOOL STUDENTS		
Adverse Experience	**Percentage of Students Reporting Experience[a]**	
	Heterosexual	**Gay, Lesbian, or Bisexual**
Threatened or injured with weapon (e.g., gun, knife, club) on school property	5.1%	10.0%
Avoided school because of safety concerns[b]	4.6%	12.5%
Cyberbullied	14.2%	28.0%
Bullied on school property	18.8%	34.2%
Forced to have sexual intercourse[c]	5.4%	17.8%
Physical dating violence	8.3%	17.5%
Sexual dating violence	9.1%	22.7%
Probable major depressive episode	26.4%	60.4%
Seriously considered attempting suicide	14.8%	42.8%
Made a suicide plan	11.9%	38.2%
Attempted suicide	6.4%	29.4%
Suicide attempt received medical care	2.0%	9.4%
[a]All rates are past-year unless otherwise stated. [b]In the past 30 days [c]Over the lifetime		
Source: [389]		*Table 7*

Gender and Sexual Minority Youth

The Centers for Disease Control and Prevention published the first-ever nationally representative survey on the health risks of gay, lesbian, and bisexual high school students in 2016 [389]. Nationwide, 88.8% of students identified as heterosexual, 2.0% as gay or lesbian, 6.0% as bisexual, and 3.2% as unsure of their sexual identity [389]. Overall, sexual minority youth are more likely than their heterosexual counterparts to experience adverse experiences and suicidality (***Table 7***).

Sexual orientation or gender identity harassment and being threatened or injured with a weapon at school are the most damaging forms of school-based victimization for sexual minority adolescents, and these factors have the greatest association with suicidality [390]. For sexual minority youth, risk factors for bullying and violence include social isolation, lack of parental support, lack of safety or support at school, and harmful norms about masculinity and femininity associated with violence against those seen as not masculine or feminine enough [389].

Bullying and violent victimization of youth perceived as violating gender norms can occur through sexual orientation-based victimization (from perceived or actual same-sex attraction) or gender-variant-based victimization (from presentation perceived to resemble gay or lesbian stereotypes) [391; 392]. Heterosexual youth whose appearance, mannerisms, or behaviors are perceived by peers as violating gender norms are also vulnerable to gender-variant-based victimization. This type of victimization is significantly associated with suicidal thoughts and behaviors in middle and high school students and potentially serious psychologic outcomes similar to those experienced by same-sex attracted adolescents [393].

Bullying and Cyberbullying

Adults are not immune to victimization from bullying or cyberbullying, but the bulk of research has focused on adolescent and young adult age groups. Bullying is defined as the use of power and aggression to control and distress another [394]. Intentionality, repetition, and abuse of power primarily distinguish bullying from other forms of aggression [395]. Cyberbullying does not induce distress through physical aggression and harm, but through the reach of Internet and social media. The emotional harm can be severe, in part from the ease that humiliating or threatening information, photos, and other content are spread, and by recruitment of other cyberbullying participants [396].

A study of 15,425 high-school students found higher rates of girls being bullied (31.3%) or cyberbullied (22.0%) compared with boys (22.9% and 10.8%, respectively). Suicide attempts were made by 4.6% of those never-bullied, 9.5% of those bullied at school, 14.7% of those cyberbullied, and 21.1% of those victimized both at school and online [397].

Peer victimization in childhood or adolescence can have long-lasting adverse effects. Among 30,436 U.S. soldiers in basic training, more frequent physical assault/theft by childhood peers was associated with increased odds of lifetime suicidal ideation and attempts; more frequent bullying comments/behaviors was associated with increased risk of ideation, planning, and attempts among ideators. Relative to non-exposure, exposure to the most persistent bullying carried a two- to fourfold increase in risk of suicidality [398].

Gender and Sexual Minority Adults

In Western countries, the lifetime prevalence of suicide attempts is 4% among heterosexuals and 17% among sexual minorities [399]. Among sexual minority populations, a history of suicide attempts increases subsequent risk of repeat attempts and fatal outcomes [377; 400]. Reports suggest high suicide attempt rates among gay/bisexual African Americans, gay/bisexual men of lower socioeconomic status, and sexual minority Latinos [401; 402; 403].

Suicidality disproportionately affects gender minorities, who may represent up to 0.5% of the adult population. Transgender men and women are roughly 5 times more likely to attempt suicide and 19 times more likely to die by suicide than cisgender adults [404]. The suicide attempt prevalence in trans populations is 22% to 43% for lifetime and 9% to 11.2% for past-year [405]. Violent victimization, experienced by 43% to 60% of transgender persons, predicts a fourfold increase in suicide risk [404]. Physical assault increases the odds of attempting suicide, but physical abuse directed at gender identity or expression has greater relative impact on suicidal behavior [404]. Experiencing fewer transphobia events has been associated with a 66% reduction in ideation and a 76% reduction in suicide attempts among ideators [405].

Armed Forces and Combat Veterans

The historically low U.S. Army suicide rate began climbing in 2004 and exceeded the civilian rate in 2009 [406]. In response, the Army invested significant resources in suicide prevention efforts [369]. Due in part to increased rates of suicide in the civilian population and increased prevention efforts within the military, the suicide rate for most years between 2011 and 2023 was similar among military and non-military personnel [375].

In one study, veterans during the Iraq and Afghanistan war era (317,581 deployed to war zones, 964,493 nondeployed) were followed from the time of discharge to 2010. With 1,868 suicide deaths, both veteran cohorts had 41% to 61% higher risk of suicide relative to the general population, but suicide risk was not associated with a history of war zone deployment and multiple deployments were not associated with greater suicide risk among deployed veterans [407].

Among U.S. Armed Forces veterans, the estimated lifetime prevalence of suicide ideation was 12.7% for men and 20.1% for women, and the prevalence of lifetime suicide attempts was 2.5% and 5.1%, respectively [408]. Among active Armed Forces suicide decedents, roughly 50% accessed health care in the month before their death and more than 25% accessed care in the week before their death. Male, never married, and non-Hispanic Black individuals were less likely to access care prior to death. The number of mental health encounters was the only predictor of suicide risk documentation among decedents at 4 weeks and 52 weeks prior to death [409].

Incarcerated Individuals

Jails and juvenile justice facilities have suicide rates higher than the national averages, and suicide is often the single greatest cause of death in correctional settings. Inmates at highest risk are young men, persons with mental illness, those who are socially disenfranchised and socially isolated, individuals with substance use disorders, those who have previously attempted suicide, gender/sexual minorities, and juveniles placed in adult correctional facilities [410]. Factors that increase suicidal risk include the psychologic effects of arrest and incarceration; intense stressors of prison life, including physical and sexual predation and assault from other inmates; and absence of formal policies for managing suicidal patients, staff training, or access to mental health care [411].

At greatest suicide risk are young (i.e., 20 to 25 years of age), unmarried, male, first-time offenders arrested for minor, usually substance-related, offences. Typically intoxicated at the time of arrest, these individuals tend to attempt suicide at an early stage of confinement, often within the first few hours, from the impact of sudden isolation, shock of imprisonment, lack of information, and fear about the future [411]. This suggests an important role for medical assessment of substance abuse and suicide proneness and inmate suicide prevention programs [31; 412].

SUICIDE AND PUBLIC PERCEPTION

Stigma often surrounds persons with suicidal behavior and suicide itself. Stigma and negative attitudes interact with postmortem determinations and media reporting, and stigma can be antecedent or consequence.

Misclassification of Suicide Deaths

Suicide determinations are not easy, even after the event, and coroners vary considerably in the verdicts they give to individuals who probably died by suicide [360]. Stigma can influence under-reporting, with families or physicians hiding evidence. Death determination may be judged by variable local standards, and ambiguous cases involving suicide may be classified "accidental" or "undetermined" deaths [413]. Context can influence how ambiguous cases of suicides are classed. Institutions such as prisons, hospitals, and religious orders may consider a suicide less embarrassing than homicide. Despite substantial doubt, declaring death a suicide can be motivated by the required investigation of homicide and apprehension of a murderer and negligence lawsuits with accidental death [413].

Suicide Reporting in the Media

Especially among youth, suicide rates may temporarily spike with intense coverage of a suicide in media reports or movies and television [414; 415; 416]. Imitation is the core factor, which is most powerfully illustrated by highly publicized suicides of celebrity figures [417].

Media coverage of suicide can misinform by attributing suicide to a single event (e.g., job, relationship loss) without acknowledging a broader context of ongoing depression, substance abuse, or lack of access to treatment for these conditions. The time from media exposure to action is brief, typically a few minutes. This gives media outlets little time for mitigating actions after population exposure to a harmful story, stressing the need to evaluate news items before publication [418]. Responsible suicide coverage can educate audiences about the causes, warning signs, treatment, and prevention of suicide [414].

Shortcomings are also found in media reporting of cyberbullying-related suicide. Few media outlets follow guidelines to protect against suicidal contagion. Few reports reference suicide or bullying prevention resources, and most suggest suicide has a single cause. A subset of reports uses individual suicides as cautionary tales to elevate cyberbullying awareness [419].

Stigma and Suicide

The stigma of mental illness and substance abuse, both closely linked to suicide, prevents many persons from seeking help over fears of prejudice and discrimination [420]. People with a substance use disorder face added stigma over prevalent beliefs that addiction is a moral failing of persons capable of controlling these behaviors [31; 421]. The stigma of suicide inhibits many from seeking treatment. Family members of suicide attempters often hide the behavior from friends and relatives, believing it reflects badly on their own relationship with the attempter or that suicidal behavior itself is shameful or sinful. These same feelings are held by many who attempt suicide [31]. Systemic, persistent stigma contributes to inadequate funding for preventive services and insurance reimbursement for treatments, perpetuates under-treatment of substance use and mental health disorders, limits access to tailored services, and maintains unnecessarily high suicide rates [31].

Holiday Suicide Myth

The idea that suicide is more frequent during the holiday season is a debunked myth partially perpetuated by the media [373]. Suicide rates are lowest in December and highest in the spring and fall [422]. The holiday suicide myth is important to counter because it provides misinformation about suicide that may interfere with prevention efforts [423].

SUICIDE MODELS AND RISK FACTORS

As discussed, the lack of predictive value for risk factors is now recognized [424]. The predictive disparity of traditional suicide risk factors (strong for ideation, poor for behavior) suggests that development of suicide ideation and movement from ideation to potentially lethal attempts are distinct processes, with distinct explanations and predictors. This has prompted efforts to identify novel, more effective risk factors guided by strong theoretical models [350; 425].

Other lines of research have identified the need to address acute and immediate factors influencing suicide risk. Many patients have long-term (i.e., one to five years) ideation or tentative planning before a suicide attempt, but almost all proximal planning occurs within two weeks and the majority occurs within 12 hours of a suicide attempt [426]. Assessment of outpatients with past-year suicide attempts and inpatients admitted for suicidality over two to four weeks showed suicidal ideation, hopelessness, burdensomeness, and loneliness varied dramatically over the course of most days in nearly all patients [427].

The suicide prevention field is in transition. Suicide risk factors, assessment tools, and risk level stratification are largely ineffective in short-term prediction of suicide but have not yet been replaced by more effective methods. Resources for suicide prevention are available from the CDC at https://www.cdc.gov/suicide/resources.

The Interpersonal-Psychological Theory of Suicide

The Interpersonal-Psychological Theory of Suicide posits that persons will not make lethal suicide attempts unless they have developed the desire (i.e., low belongingness, high burdensomeness) and ability to do so [377]. Thwarted belongingness is defined as the experience of having little or no social connectedness, a result of living alone, death of a spouse, or disabling physical or psychiatric illness. The need to belong is a core aspect of human nature; when unfulfilled, suicide risk increases [428]. Perceived

burdensomeness is evident when persons feel their family members and the world in general would be better off if they were no longer living, and this can initiate suicidal ideation [428]. Acquired capability for suicide refers to reaching the point at which a patient overcomes his or her innate fears of pain, injury, and death with suicide. Opponent process theory suggests with repeated exposure, the effects of previously noxious, aversive, or provocative stimuli may recede, and the opposite effect of the stimuli becomes strengthened and amplified [429]. Persons can habituate to pain, injury, or death through previous suicide attempts, exposure to trauma, armed combat, violence, or death and diverse experiences related to psychologic and physical pain [350; 351].

The Cubic Model

The cubic model defines psychologic pain—psychache—as one of three essential dimensions in suicide risk (along with stress and perturbation) [430]. Psychache often underlies the desire to escape from unbearable pain and represents a state of anguish sufficiently aversive to over-ride innate fears of pain, injury, and death [351]. Psychologic pain distinguished attempters from ideators among 378 adults with history of suicidality [350].

Non-Suicidal Self-Injury

Non-suicidal self-injury (NSSI) is intentional, non-socially accepted damage to the bodily surface, without suicidal intent, by cutting, scratching, hitting/banging, carving, or scraping. Roughly 17% to 18% of teens have one or more NSSI event; up to 60% of adolescent psychiatric patients have one NSSI event and 50% have repetitive NSSI [431; 432]. NSSI prevalence is higher in girls and women. It rises from late childhood to early adolescence, peaks in mid- to late-adolescence, and generally declines by young adulthood [383]. NSSI can occur without a psychiatric diagnosis [433].

NSSI serves as a means to escape aversive emotional (e.g., sadness, anxiety) or cognitive (e.g., negative thoughts or memories) states, relieve tension or anger, or regain perception of control [383; 434]. Adolescents with repetitive NSSI remain at high risk of dysfunctional emotion regulation strategies after ceasing the behaviors and show increased substance abuse as the behaviors decrease [435]. Those who cut themselves on body areas other than arms or wrists have the greatest risk of subsequent suicide [436]. Identifying with "goth" or "emo" youth subculture, sexual minority status, social media exposure to self-injury behaviors, bullying, and childhood emotional abuse are risk factors for NSSI [437].

There is a temporal relationship between nonsuicidal and suicidal self-injury in adolescent outpatients and inpatients. On average, suicide ideation occurs before initial NSSI behavior, suggesting that pathways to NSSI and suicidal behavior may occur simultaneously rather than sequentially from nonsuicidal to suicidal self-injury. The transition from nonsuicidal to suicidal self-injury is relatively fast, and a key period for intervention and prevention is within the first 6 to 12 months after the onset of suicidal thinking [438].

Chronic Pain

Chronic uncontrolled pain is second only to bipolar disorder as a medical cause of suicide [439; 440; 441]. The distress, exhaustion, and hopelessness of chronic unrelieved pain can invite intended overdose. Death is no longer feared, but instead becomes a welcome prospect of permanent relief from suffering and anguish [442]. Individuals with physical pain are substantially more likely than those without pain to report lifetime death wish; to have current and lifetime suicidal ideation, plans, and attempts; and to die from suicide. Chronic uncontrolled pain is a consistent risk factor for suicidality, even after controlling for demographics and psychiatric and substance use disorders [443; 444].

The perception of being a burden significantly predicts wishing to die, active suicide ideation, presence of a suicide plan, history of suicide attempts, and preference for death over disability in patients with chronic pain [445]. Chronic uncontrolled pain elevates the risk of suicide to escape unbearable suffering, in part by promoting (or becoming amplified by) depression and hopelessness. This intensifies a desire to escape that erodes the natural fear of dying, promoting the development of fearlessness about death—a key risk factor for suicide [446].

Psychologic Pain

Suicide is viewed as behavior motivated by the desire to escape from unbearable pain, and suicide risk research implicates two related constructs: psychache and pain tolerance, defined as the greatest duration or intensity of painful stimuli one can withstand before pain is intolerable and unbearable [447; 448]. Psychache is a crucial link between suicidal risk and behavior and mediates the relationship between depression or other psychologic conditions and suicidality [447; 448; 449; 450; 451]. As discussed, numerous studies indicate that psychache highly predicts suicidality and distinguishes attempters from ideators. Changes in suicide preparation and intent over three years significantly correlates with changes in psychache but not depression or hopelessness [452]. Evidence links pain tolerance to self-injurious behaviors and suicide risk. Psychache and physical pain are linked to other predictors of suicide, including impaired reward processing, hopelessness, and depression [448].

Mental pain is a uniquely intolerable experience that exceeds the sum of negative emotions, thoughts, and sensations. Beliefs can develop that change or improvement is not possible and self-destruction is the only resolution [447; 453]. Unbearable, persistent psychologic pain is also thought to reduce awareness of the body and its signals, making it more likely to perceive the body as an object and an easier target to attack [454].

Among patients in residential treatment with serious psychopathology, history of suicide ideation or attempts is associated with proportionally greater psychic pain and fewer reasons for living. Treatment of such patients should include both an understanding of the sources of psychic pain and promotion of individual discovery of reasons for living [455].

Psychiatric Disorders

Traditional suicide risk factors include mood (e.g., bipolar disorder, MDD), anxiety, impulse control, personality, psychotic, and alcohol/substance use disorders [368]. There is little evidence that trait impulsivity increases risk of attempts in ideators, although suicidal behavior can occur during transient impulsive states [456]. In patients with MDD (the condition most associated with suicide), the lifetime suicide prevalence is 4% for hospitalized individuals, 2.2% in mixed inpatient/outpatient populations, and 8.6% if hospitalized for suicidality [66]. However, it is important to remember that MDD alone does predict acute risk of suicide, and depression and most psychiatric disorders alone do not predict transition from ideation to suicidal plans or attempts.

Acute Anxious Agitated Distress

While symptomatic panic disorder, PTSD, and generalized anxiety disorder influence suicide behavior more than any other psychiatric disorders, it is the acute state of anxious agitated distress (not an anxiety disorder diagnosis) that greatly increases risk of ideators moving to suicide attempts [368; 457]. Among inpatient suicides, 79% met diagnostic criteria for severe or extreme anxiety and/or agitation.

Anxious agitated distress is characterized by intense/severe anxiety, agitation, or panic and mental anguish and unrest with restless or repetitive behaviors, heightened arousal, expressions of emotional turmoil, irritability, anger outbursts, insomnia, and nightmares [351; 368; 409; 458; 459]. It is commonly observed immediately before suicide and is

a documented precursor of near-fatal attempts. Clinicians should inquire regarding perceived anxious agitated distress and may ask patients if they feel like "jumping out of their skin" or "going to explode" or if feel they must "take action" or "do something" from overwhelming inner restlessness.

Bipolar Depression

An estimated 5 to 10 million Americans currently suffer from bipolar disorder. Bipolar depression is the depressive phase of bipolar disorder, when suicidal behavior is most frequent but least responsive to standard treatment. On average, patients with bipolar disorder spend three times longer in the depressive phase than in the manic phase. It is a highly disabling disorder, causing marked occupational and social impairment. Patients with bipolar depression have a 25% to 56% lifetime prevalence of suicide attempts, and 10% to 19% die by suicide [460].

Alcohol and Substance Use Disorders

More than 33% of suicides occur during alcohol use, typically at high levels of ingestion, and controlled trials confirm that acute alcohol use is a potent suicidal risk factor [461; 462; 463; 464]. Alcohol intoxication significantly increases suicide risk and may heighten psychologic distress and aggression, encourage suicide attempts, and inhibit adaptive coping strategies [465]. During intoxication, disinhibition facilitates movement from ideation to impulsive action, and alcohol intoxication predicts use of lethal means in suicide [465; 466]. However, substance use disorder and suicidality can be temporarily linked, as patients are likely to deny suicidality after intoxication has resolved [467; 468].

Psychotic Disorders

Suicide is the greatest cause of premature death in individuals with schizophrenia, with the highest risk in young, unemployed men. Other risk factors include recurrent relapses, fears of deterioration in persons with high intellectual ability, positive symptoms of suspiciousness and delusions, and depressive symptoms [469; 470]. The suicide risk is greatest during early-stage illness, early relapse, and early recovery; risk declines with prolonging illness duration [469; 470].

Persecutory panic (a state of terror often associated with command hallucinations and delusions) has been observed in many psychotic disorders. These patients are described as terrified of a threatening and imminent annihilation or dismemberment, imagine that suicide is survivable, and desperately attempt to escape from the danger of imaginary menace by suicide [471]. Therefore, the presence of persecutory panic is considered a risk factor for suicide and should be addressed immediately.

SUICIDE MEANS AND METHODS

In 2024, firearms were the most common means used in suicide deaths (56.5%), followed by suffocation/hanging (23.5%), other (11%), and poisoning (9%) [373; 374]. In the United States, the rate of suicide by firearm is eight times greater than the rates in other economically developed countries [472]. Household gun ownership strongly correlates with firearm suicide, and storage practices impact suicide rates, which are higher in geographic areas with greater household prevalence of loaded guns. The presence of loaded, unlocked firearms within reach is a risk factor for fatal outcomes from suicidal behavior [473]. Firearm suicides reached an all-time high in 2024, increasing 13% since 2020 [373].

Suicide by cop is defined as an event in which a suicidal subject intends to die and, aware of the finality, directs behavior against police that is sufficiently life-threatening to compel a deadly force response [474]. Although usually intending to die, the subject is ambivalent about taking his or her own life. Suicide by cop victimizes the suicidal subject and the police, who are often placed in difficult situations. In 707 officers-involved shootings between 1998 and 2006, 36% were attempted suicides and 51% of subjects were killed [475]. Suicide by cop is characterized by one of the following [475; 476]:

- Direct confrontation: The attack on police is premeditated with intent to die from a deadly force response.
- Disturbed intervention: Emotionally disturbed behavior that draws police intervention, without evidence of wanting police involvement.
- Criminal intervention: A criminal, believing there is no way out, prefers death to arrest and incarceration.

SUICIDE MOTIVATION

Most suicides and attempts are driven by the motivation to escape unbearable pain. Other motives include revenge, shame, humiliation, delusional guilt, command hallucinations, gaining attention or reaction from others, loneliness, self-hatred, or a sense of being a burden, not belonging, feeling trapped, or having no purpose [364]. Individuals have a unique balance between their personal motivations for suicide and their reasons for living. Reasons for living can include religious beliefs, a sense of responsibility to children or others, plans for the future, or a sense of purpose in life. A strong social support network is also protective against suicide [364]. Importantly, "reasons for living" become irrelevant when suicidal intent is moderate or greater.

SUICIDE PREVENTION

Large-scale suicide prevention efforts in the United States began in 1958 with the first suicide prevention center in Los Angeles, followed by nation-wide crisis intervention centers [31]. The risk factor approach to suicide prevention was introduced in 1966; organizations and national strategies were established to further these efforts. Survivors of suicide started the Suicide Prevention Advocacy Network USA (SPAN USA) in 1996 to campaign for a national suicide prevention strategy, prompting the creation of the National Strategy for Suicide Prevention (NSSP) in 2001 [477].

Recognizing that decades of suicide prevention research has not decreased suicides, the NSSP partnered with the National Action Alliance for Suicide Prevention in 2012 to develop national priorities for suicide prevention science. Suicide research was prioritized to delineate promising research pathways toward a set of 12 "aspirational goals" considered areas of focus necessary for preventing substantial numbers of suicide deaths and attempts [478].

The revised NSSP was launched in 2013, elaborating on methods for systemic change in healthcare delivery, public and media conversations around suicide and suicide prevention, the timeliness and utility of suicidality surveillance data, prevention, and clinical care [479]. "Zero suicides" is an aspirational goal based on the belief that suicide of patients receiving care in any setting is preventable, and one area of commitment is to program approaches that prevent suicidal patients from failing to receive adequate care. In 2014, the NSSP launched the Framework for Successful Messaging, which outlines how individuals working in suicide prevention and behavioral healthcare fields can create hopeful messaging to help save lives. In 2015, the NSSP and partners offered a three-panel series focused on suicide in middle-aged men, teenagers and technology, and military personnel/veterans [479]. Universal suicide risk screening in primary, specialist, and emergency care settings was recommended [480].

Suicide Prevention in the Elderly

The elevated suicide risk in the elderly is influenced by the prevalence of isolation, chronic pain, chronic illness, and/or depression (often undiagnosed). Many at-risk elderly adults suffer from intense loneliness, bereavement, or loss of social roles; fears of disability, dependency, or burdensomeness to others are common [481]. Enhancing connectedness to others is a suicide protective factor and formal strategy to prevent suicide in the elderly [480].

TREATMENT OF SUICIDALITY

Psychotherapy

Highly structured, problem-solving, coping-oriented psychotherapies have the greatest research support for effectively treating suicidal risk, and include dialectical behavioral therapy, cognitive therapy, and collaborative assessment and management of suicidality [482].

Dialectical behavioral therapy is the most thoroughly studied and effective psychotherapy for suicidal behavior. It has been shown in multiple studies to decrease suicide attempts, self-harm, and other suicide-relevant markers such as suicidal ideation and hopelessness. This psychotherapy emphasizes skills training and mindfulness-based emotion regulation [482].

Cognitive therapy is the next most studied and supported suicide-relevant psychotherapy. The initial randomized controlled trial of suicide-specific cognitive therapy in persons presenting to the emergency department with suicide attempt gave convincing evidence that 10 sessions decreased follow-up suicide attempts compared to the control group. The primary focus of this modality is identification of patient "suicidal mode," activated by certain experiences, memories, thoughts, and situations. Patients learn what triggers their suicidal mode and develop and use alternate non-suicidal coping responses [482].

Collaborative assessment and management of suicidality is a therapeutic framework that emphasizes collaborative assessment, crisis response planning, and problem-focused interventions designed to identify and treat the "drivers" of suicidal risk. In one study, it was shown to effectively treat suicidal ideation, overall symptom distress, hopelessness, and reasons for living at 12-month follow-up compared to enhanced usual care [482].

Pharmacotherapy

Effective pharmacotherapy for suicidality has been elusive. Antidepressants are standard treatment for acutely suicidal patients, but delayed onset imposes unacceptable distress and elevates risk of lethal self-harm [47]. In MDD and bipolar disorder, lithium is protective against suicidal behavior and has extensive evidence support, but it is underprescribed for this purpose. In schizophrenia, clozapine is superior to other antipsychotic agents in lowering suicide rates. However, the need for close toxicity monitoring has limited its use in preventing suicide. In severe MDD with high suicide risk, ECT is established as rapid, effective treatment, but practical issues and stigma constrain its use [47; 483; 484].

Aside from clozapine and lithium, pharmacotherapy approaches have traditionally been based on the belief that suicidality is an extension of MDD [485]. However, breakthroughs have been made in rapid-active drug interventions for suicidal individuals, with ketamine, esketamine, and buprenorphine now being explored for this use [485; 486; 487; 488; 489; 490; 491]. In 2016, the FDA granted breakthrough therapy designation for intranasal esketamine in patients with MDD at imminent risk for suicide [321]. A study published in 2020 found that esketamine nasal spray demonstrated rapid and robust efficacy in reducing depressive symptoms in severely ill patients with MDD who had active suicidal ideation with intent [492].

ASSESSMENT OF SUICIDE RISK

Standard suicide risk assessment intends to gather clinical information sufficient to determine patient risk level for suicide, culminating with clinician estimation of risk based on suicide thoughts, intent, behaviors; protective and risk factors, precipitants, warning signs; and behavioral observation during assessment [364; 366; 368]. Patients with any of the following conditions should be assessed for suicide risk, although many are nonspecific factors that do not predict current risk [364; 366; 368]:

- Psychiatric (e.g., MDD, bipolar depression, schizophrenia, PTSD) and medical (e.g., chronic pain, sleep disturbance, frequent headaches) disorders
- Positive depression screening results (e.g., very high scores, suicidality concerns, suicidal thoughts in perinatal women)
- Patients seeking help or self-reporting suicidal thoughts
- Referrals from close others over concerns about patient behavior
- Clinical judgment

Eliciting Information

Guidelines recommend an empathetic and direct, yet objective and non-judgmental, approach to eliciting information from patients believed to be at risk for suicide. The gravity of high acute suicide risk and vital need for information suggests an assertive approach. The following recommendations have been made for these situations [364; 493]:

- Be clear and use specific, open-ended questions. Be flexible to frame questions more clearly.
- Avoid assuming patients and families understand clinical terms, even if clarification is not requested.
- Ask for clarification, and do not accept vague answers. Ask follow-up questions.
- Document positive and negative specifics carefully, in narrative form.

Clinical suicide assessment guidelines give little attention to dealing with patients suspected of being at acute risk for suicide who are unable or unwilling to cooperate with the risk assessment process. Patients evaluated for suicide are often in crisis and may fear that sharing their suicidality will result in loss of autonomy through hospitalization, behavioral restriction, or loss of esteem from a psychiatric diagnosis. In response to these fears, patients can minimize or deny their suicidality when directly asked or make statements to decrease clinician vigilance; clinicians should be aware of these tactics [366].

Thinking and cognition are often clouded, and intentionally or not, many patients with increased suicide risk give inaccurate, incomplete, and unreliable histories. Patients can misunderstand their symptoms, condition, and risk and usually cannot predict their impulses and behaviors [493; 494]. Clinicians often believe suicidal patients view them as allies, but they are more likely seen as adversaries with conflicting goals: preserving versus ending life. This is a fundamental change in the patient-provider relationship after a patient decides to attempt suicide [494].

As such, alternative lines of evidence may be necessary to confirm suspicions of suicide risk, including obtaining objective evidence and collateral information/permissions [493; 494]. Patients who attempt suicide may communicate intent to relatives before clinicians [494]. Among inpatients who die by suicide, 78% denied suicidal ideation in their last communication with staff, 60% told their spouse, and 50% told other relatives; however, only 18% told their physician [459]. Other providers, relatives, and close others can be vital information sources to help ascertain acute suicide risk level and are often more reliable than severely suicidal patients.

ACUTE SUICIDE RISK LEVEL AND INTERVENTION			
Risk Level	**Contributing Factors**	**Suicidality Level**	**Possible Interventions**
High	Acute, severe psychiatric illness or symptoms Acute precipitating event	Lethal attempt Ideation, strong intent to act/plan Cannot control impulses Rehearses/prepares suicide	Continuous observation; limit access to lethal means; immediate transfer to emergency department for hospitalization
Moderate	Multiple warning signs or risk factors	Ideation No intent to act Impulse control intact	Prompt referral to mental health clinician Limit access to lethal means
Low	Risk factors modifiable Protective factors strong	Ideation No plan, intent, behavior	Outpatient referral Give emergency/crisis numbers

Source: [364; 366; 368] *Table 8*

Assessing Suicidality

As discussed, many areas of patient information emphasized by standard practice guidelines as crucial for patient risk assessment have been found to lack risk prediction value. Instead, clinicians should focus on critical factors related to suicide risk, identified by studies of callers to suicide prevention hotlines, including [493; 495]:

- Suicidal desire: Suicidal ideation, psychologic pain, hopelessness, helplessness, perceived burden to others, feeling trapped, feeling intolerably alone
- Suicidal capability: History of suicide attempts, exposure to someone else's death by suicide, available means of killing self/others, current intoxication, substance abuse, acute symptoms of mental illness, extreme agitation/rage
- Suicidal intent: Attempt in progress, plan to kill self/others, preparatory behaviors, expressed intent to die

Suicide Warning Signs: Indications for Urgent/Immediate Action

Suicide warning signs are recent, unusual changes in the patient, often an acute response to precipitants, and proximally associated with imminent suicide risk. Intent may be signaled through emotions, thoughts, or behaviors. Danger is elevated with previous suicide attempts, family history of suicide, or possession of a lethal method. Presence of any of the following warning signs requires immediate attention, mental health evaluation, and possibly hospitalization to ensure patient safety, stability, and security:

- Suicide communication—threatening to harm or kill self
- Preparations for suicide
- Seeking access, or recent use, of lethal means

Other warning signs may further elevate acute suicide risk include [366; 368]:

- Verbalizations: Hopelessness (feeling of defeat, that nothing can improve their situation), purposelessness (sense of purpose or reason to live is absent), feeling trapped (no way out, no escape possible), or guilt/shame (overwhelming self-blame, remorse, self-hatred)
- Behaviors: Anger, rage, revenge-seeking, reckless/impulsively risky behavior, marked mood changes, anhedonia, withdrawal from family, friends, society
- Inability to sleep
- Command hallucinations

Acute Suicidality Risk Level and Intervention

After a patient's suicide risk level has been assessed and assigned, based on clinical judgment, the level of intervention may be selected (***Table* 8**).

The Cognitive State

The cognitive/affective state of suicidal patients is typified by ambivalence, impulsivity, and rigidity. The desire to die and live alternates; clinicians may explore ambivalence to reinforce reasons for living. The transient nature of impulse permits clinicians to defuse a suicide crisis by support at an impulsive moment. Rigidity constricts patient thinking, mood, and motivation; perception of problems and outlook is dichotomized into black-and-white reasoning. With gentle reasoning, clinicians may help the patient understand and consider alternative options to death [469; 470].

Acute Anxious Agitation

Treat patients with anxious agitated distress states aggressively with benzodiazepines and/or antipsychotics, considering age and past/current medication exposure. Frequently monitor these patients for efficacy and side effects, and strongly consider emergency evaluation [368; 496].

Safety Precautions

In all clinical settings, scrutinize patient belongings and nearby medical equipment, such as intravenous tubing, for use in self-harm. Decline family or friends' insistence on driving patients to treatment; transfer patients for emergency evaluation or hospitalization safely by ambulance with trained personnel following standard protocols. During hospital or emergency department discharge or outpatient visits, recommend that close others secure or remove firearms, large quantities of medication, and other obvious means of self-harm. Make an effort to involve family and significant others in crisis planning and treatment [368].

Suicide Prevention Contracts

Written and verbal "no harm" and "no-suicide" contracts do not prevent suicide and tend to give clinicians a false sense of safety that decreases vigilance and may communicate an uncaring "brush-off" to patients, especially in busy clinics and emergency departments. In one study, approximately 50% of inpatients who died by suicide had a prevention contract in place. It is recommended that suicide prevention contracts not be used [366; 493; 497; 498; 499].

SUICIDE LOSS SURVIVORS

Suicide loss survivors are those family members and friends affected by the death of a loved one through suicide. Estimates suggest that each suicide death exposes 135 people, of whom 6 or more experience a major life disruption. With 1,005,397 suicide deaths in the United States between 2000 and 2024, there are more than 6 million suicide loss survivors [374].

The death of a loved one by suicide can be shocking, painful, and unexpected for survivors, with significant impact on health and mental health. A Danish study found that within five years of the loss, spouses bereaved by a partner's suicide had higher risks for mental disorders, suicidal behaviors and mortality, use of public assistance, and mental health care utilization than spouses bereaved by other manners of death [500]. The ensuing grief can be intense, complex, chronic, and nonlinear.

Working through grief is a highly individual and unique process that survivors experience in their own way and at their own pace. Grief does not always move in a forward direction, and there is no timeframe for grief. Survivors should not expect their lives to return to their previous state and should strive to adjust to life without their loved one. The initial emotional response may be overwhelming, and crying is a natural reaction and an expression of sadness following the loss of a loved one [481].

Survivors may struggle to comprehend why the suicide occurred and how they could have intervened, and the guilt over perceiving missed opportunities with hindsight can be agonizing. Relief may be felt if the loved one was prone to difficult mood or temperament. The stigma and shame surrounding suicide may inhibit family members and friends from contacting survivors and can prevent survivors from reaching out for help. Ongoing support remains important to maintain family and relationships during the grieving process [481].

Many survivors find support groups for suicide loss survivors the most beneficial means to feel supported and understood. The shared experience of group members enables survivors to openly discuss their story and feelings without pressure, fear of judgment, or shame [481].

The American Foundation for Suicide Prevention maintains an international directory of suicide bereavement support groups on their website at https://afsp.org/find-support.

CONCLUSION

Depression is a debilitating and potentially life-threatening mood disorder that afflicts millions of Americans. Depressed persons are more likely to develop chronic medical conditions, including type 2 diabetes and cardiovascular disease, and depression is projected to be the leading cause of disability over the next 20 years. Furthermore, suicide is a major preventable public health problem and cause of mortality. Depression, especially with comorbid substance abuse, represents a significant risk factor for suicide. Depression causes enormous pain and suffering to the afflicted and substantial economic cost to society, and the emotional impact on survivors of a depressed person who has died by suicide is often devastating. Many persons with depression do not seek treatment; among those who do, only a fraction receive treatment consistent with current practice guidelines. Primary care contact may represent the last opportunity for intervention in the severely depressed suicidal patient, making the thorough comprehension of identification and treatment of depression and suicide risk imperative.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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