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In the Clinic®

Depression

Most psychiatric care is delivered in primary care settings, where depression is the most common presenting psychiatric symptom. Given the high prevalence of depression worldwide and the well-established consequences of untreated depression, the ability of primary care clinicians to effectively diagnose and treat it is critically important. This article offers up-to-date guidance for the diagnosis and treatment of major depressive disorder, including practical considerations for delivering optimal and efficient care for these patients.

Screening

Diagnosis

Treatment

Practice Improvement

CME/MOC activity available at Annals.org.

Physician Writers
Robert M. McCarron, DO
Bryan Shapiro, MD, MPH
Jody Rawles, MD
John Luo, MD
University of California, Irvine, Irvine, California

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Depression is a mood disorder characterized by a persistent feeling of sadness and/or an inability to experience pleasure, with associated deficits in daily functioning. Worldwide, depression is a leading cause of disability and years of productive life lost (1). The global economic cost associated with depression is expected to nearly double by 2030 (2), yet analyses have identified a return of $4 for every $1 spent on depression care (3). In the United States, prevalence ranges from 5%–10% but can be as high as 40%–50% in certain primary care or specialty settings (4). Only about half of depressed persons receive adequate treatment despite the existence of high-quality, evidence-based therapies (5).

Depression significantly affects the prevalence, cost, and outcomes of many common general medical comorbidities, such as diabetes (6). It is also the leading risk factor for suicide, and suicide rates in the United States have increased by roughly 35% since 1999 (7). Major depressive disorder (MDD), the focus of this article, is a highly prevalent subtype of clinical depression that is frequently encountered in primary care settings. Its screening, diagnosis, and management may seem overwhelming for some primary care clinicians, but it is closely tied to successful management of general medical conditions and optimization of overall well-being.

Screening

Which patients are at especially high risk for MDD?

The pathophysiologic cause of depression is unknown, and no clinically useful biological diagnostic markers or biological screening tests are currently available. However, several known risk factors warrant consideration, such as low socioeconomic status; comorbid chronic medical conditions, such as diabetes, cardiovascular disease, or obesity; and a personal or family history of MDD (see the **Box:** Risk Factors for MDD) (8).

Should clinicians screen for MDD?

The 2016 U.S. Preventive Services Task Force guidelines recommend screening all adults, including pregnant and postpartum women as well as older adults, for MDD, provided that adequate resources for diagnosis, treatment, and appropriate follow-up are available (9). Screening is also recommended in adolescents aged 12–18 years. It can be useful in patients who have risk factors for depression (**Box:** Risk Factors for MDD) or present with unexplained somatic symptoms, chronic pain, anxiety, substance misuse, or nonresponse to effective treatments for medical conditions (10).

A meta-analysis of screening studies suggested that screening for MDD is associated with a 9% absolute reduction in the proportion of patients with persistent depression at 6 months. Assuming a prevalence of 10%, 110 primary care patients would need to be screened to produce 1 additional remission (11).

The absolute reduction and therefore the utility of screening for

Risk Factors for MDD

- Alcohol dependence
- Childhood trauma
- Chronic medical conditions
- Female sex
- Low socioeconomic status
- Older age
- Personal or family history of depression
- Recent childbirth
- Recent stressful events

PHQ–2 Screen for Depression

Questions:

- "Over the past 2 weeks, have you felt down, depressed, hopeless?"
- "Over the past 2 weeks, have you felt little interest or pleasure in doing things?"

Scoring: 0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day

Total score = sum of 2 item scores

MDD is highly dependent on the prevalence of the illness in the population being assessed. Although the optimal interval for MDD screening is not well established, annual screening seems reasonable given the high worldwide prevalence of depression and the ease with which screening can be implemented.

What screening methods should clinicians use?

A score of 2 or higher on the Patient Health Questionnaire 2 (PHQ-2) instrument (see the **Box:** PHQ-2 Screen for Depression) has a sensitivity of 86% and a specificity of 78% for diagnosing MDD in primary care settings (12). Patients screening positive on the PHQ-2 should have a more complete assessment to determine whether they meet the criteria for MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (8). The PHQ-9 is a diagnostic and severity rating instrument that can be used after a positive result on the PHQ-2 (13). Compared with the Beck Depression Inventory, the PHQ-9 is shorter, is more freely available, and is based more closely on diagnostic criteria for MDD but has similar psychometric properties (14). A PHQ-9 score of 10 or higher has a sensitivity of 74% and a specificity of 91% in primary care settings (12).

A 2020 meta-analysis of 100 studies found that the combination of a PHQ-2 (cutoff score of ≥2) followed by a PHQ-9 (cutoff score of ≥10) if screening positive reduced the number of participants needing to complete the full PHQ-9 by 57% compared with using the PHQ-9 alone (13).

Screening... Clinicians should screen for MDD as the first step in a systematic evaluation of mood disorders in all adults. Established risk factors for MDD should be considered. The PHQ-2 and PHQ-9 are efficient and widely used tools for depression screening in primary care settings.

CLINICAL BOTTOM LINE

Diagnosis

What are the diagnostic criteria for MDD?

MDD is diagnosed when 5 or more DSM-5 symptoms occur in the same 2 weeks with a change from previous functioning (**Table 1**) (8). One symptom must be either depressed mood or anhedonia. The DSM-5 diagnostic criteria do not indicate severity. Only a focused clinical assessment or a validated depression screening tool can determine the severity of a depressive episode.

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Table 1. **Diagnostic Criteria for Major Depressive Disorder, Based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition****

A. Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either depressed mood or loss of interest or pleasure. (**Note:** Do not include symptoms that are clearly attributable to another medical condition.)

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all or almost all activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiologic effects of a substance or another medical condition.

Note: Criteria A to C represent a major depressive episode (MDE).

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of an MDE in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

In distinguishing grief from an MDE, it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in an MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves (the so-called pangs of grief). These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of an MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of an MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in an MDE. In grief, self-esteem is generally preserved, whereas in an MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in an MDE such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

D. The occurrence of the MDE is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode. (**Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiologic effects of another medical condition.)

The DSM-5 retained the core diagnostic criteria for MDD and the requisite symptom duration of at least 2 weeks described in the DSM-IV. Premenstrual dysphoric disorder and persistent depressive disorder (formerly dysthymic disorder) are included as specific types of depression. Two new specifiers ("mixed features" and "anxious distress") for MDD were included in the DSM-5. "Mixed features" indicates the coexistence of a major depressive episode and up to 3 hypomanic or manic symptoms while not meeting full bipolar spectrum diagnostic criteria. "Anxious distress" allows the clinician to rate

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Table 2. **Patient Health Questionnaire–9***

Over the past 2 weeks, how often have you been bothered by any of the following problems? (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day)

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people have noticed, or the opposite (i.e., being so fidgety or restless that you have been moving around a lot more than usual)
9. Thoughts that you would be better off dead or hurting yourself in some way
10. If you have checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
** Items 1 through 9 are summed to yield a score of depression severity that ranges from 0–27. On this scale, 0–4 is "none," 5–9 is "mild," 10–14 is "moderate," 15–19 is "moderately severe," and 20–27 is "severe." The first 9 items reflect the DSM-5 criteria, and item 10 assesses functional impairment. This scale can assist in the DSM-5 diagnosis of major depressive disorder and quantifies depression severity. Like symptom severity, severe functional impairment may suggest the need for hospitalization and psychiatric consultation.*

the level of anxiety in the context of a discrete MDD.

The differential diagnosis for MDD is broad. A major depressive episode occurring in a patient who has experienced a prior hypomanic or manic episode or manic symptoms occurring concurrently with the depressive episode ("a mixed episode") defines a bipolar spectrum disorder (8). Manic or hypomanic episodes can be identified as distinct, abnormal periods of elevated, expansive, or irritable mood and increased goal-directed behavior or energy with associated symptoms, such as decreased need for sleep, racing thoughts, or inflated self-esteem (8). In a patient presenting with acute major depression, it is important to exclude prior manic or hypomanic episodes because use of unopposed antidepressants in acute bipolar depression is unlikely to be effective and may induce frank mania, anxiety, irritability, and dysphoria. Bipolar depression is typically treated with atypical antipsychotics and/or mood stabilizers.

MDD can be distinguished from normal sadness by duration (for example, for 2 weeks, most of the day, or nearly every day), symptoms (≥5 depressive symptoms), and degree of associated distress or functional impairment. An adjustment disorder with depressed mood, a condition that occurs in response to an acute psychosocial stressor, does not meet full criteria for MDD and often does not require pharmacologic treatment. Of note, bereavement is no longer an exclusion criterion for the diagnosis of MDD. Depressive episodes that are considered to be a direct pathophysiologic consequence of a medical disorder or directly due to the effects of a substance are secondary depressive disorders distinct from MDD (8).

Although there are no clear age- or gender-related differences in illness course or treatment response in MDD, younger persons with depression may be

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more likely to have symptoms of hypersomnia and hyperphagia, whereas older persons may be more likely to have melancholic features, such as psychomotor retardation or lack of emotional reactivity. Women are at higher risk of attempting suicide, but men are at higher risk of completing suicide (8).

How can clinicians determine the severity of depression?

In addition to a focused clinical interview, patient- and clinician-rated scales can help determine depression severity and assist in monitoring treatment response. The PHQ-9 is easily scored to quantify the severity of MDD and is recommended in primary care settings (**Table 2**) (15). In addition to suicidality, severe functional impairment, such as inability to provide basic self-care, may suggest the need for psychiatric consultation or hospitalization (16).

How should clinicians assess a depressed patient's risk for self-harm, including suicide?

Each year, more than 40 000 U.S. citizens die by suicide. Between 1999 and 2018, the age-adjusted suicide rate in the United States increased by 35%, most notably between 2006 and 2018 (7). Mental health conditions and addictive disorders, such as alcohol use disorders, are the strongest risk factors for suicide in all age groups; they are present in more than 90% of persons who complete suicide (17). In patients with major depression, previous suicide attempts are the best predictor of completed suicide (18). Most patients who die by suicide have seen a physician in recent months (19). Clinicians should assess acute risk for suicide at each visit for depression by asking the patient directly about suicidal thoughts, intent, or plans. In addition, consideration of risk factors and collateral history is important.

More than 50% of men who complete suicide do so with a firearm (20). Rates of firearm and nonfirearm suicide vary markedly by ethnicity and state (21). Asking about and reducing access to lethal means (especially firearms) can reduce suicide risk (22). Close telephone follow-up by an experienced psychiatrist or another qualified mental health provider can reduce suicide risk after a previous attempt (23). Accurate assessment of suicide risk and the need for hospitalization is critical. A psychiatrist should be consulted for any uncertainty about either acute or chronic suicide risk.

When should clinicians consult a mental health professional for help diagnosing depression or a related mood disorder?

Although many mood disorders can be successfully managed by primary care clinicians, psychiatric consultation should be considered for diagnostic uncertainty, psychiatric comorbid conditions, significant risk for suicide, or suboptimal response to treatment. It is critically important for the primary care provider to screen for comorbid anxiety, psychosis, mania or hypomania, and ongoing substance misuse. Psychiatric evaluation is warranted if these conditions are present and severe.

Clinicians may also consider general medical causes of depression before initiating a behavioral health referral. A targeted medical history and physical examination are indicated if MDD is suspected. Thyroid abnormalities, adrenal insufficiency, electrolyte abnormalities, nutritional deficiencies, and inappropriate use of opioid medications may cause depressive symptoms. Substances that may induce depressive episodes, such as corticosteroids, interferon-α, or isotretinoin, should also be considered.

Diagnosis... The DSM-5 criteria are the standard for diagnosing MDD. The risk for suicide and comorbid mental and physical illness should be assessed in each patient. If clinicians are uncertain about a patient's diagnosis, suicide risk, or need for hospitalization, psychiatric consultation is highly recommended.

CLINICAL BOTTOM LINE

Treatment

How should clinicians approach pharmacologic and nonpharmacologic treatment of MDD?

Initial treatment of MDD may involve antidepressant medication, psychotherapy, or a combination of both. Complementary, alternative, and exercise treatments may also be used but have a more limited evidence base (24, 25). Factors that influence the initial treatment approach include patient preference, prior treatment experiences, and depression severity. The presence of interpersonal problems, psychosocial stressors, or comorbid personality disorder suggests the need for psychotherapy. Therapist availability and insurance coverage limitations are often barriers to accessing psychotherapy. Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) are the most evidence-based forms of psychotherapy in the acute treatment of MDD, although psychodynamic psychotherapy and problem-solving therapy (PST) may also be used (26).

In accordance with practice guidelines from the American Psychiatric Association, medication should be prescribed for patients with severe MDD (PHQ-9 score ≥20) given the stronger evidence of efficacy in this subgroup (26, 27). Either medication or psychotherapy may be used in mild or moderate MDD, and a combination of both may be used in moderate or severe MDD (26).

Exercise may be appropriate for milder forms of depression, though close follow-up is needed (26). Combined treatment (pharmacotherapy with psychotherapy) shows no short-term benefit, although psychotherapy may protect better against relapse (28, 29). For example, Biesheuvel-Leliefeld and colleagues found that psychotherapy, including different forms of CBT, IPT, and PST, prevented relapse better than usual care or antidepressant monotherapy (30).

The American College of Physicians updated its practice guidelines to recommend CBT or second-generation antidepressants as initial treatment of mild to severe MDD after a thorough discussion of risks, treatment benefits and costs, accessibility, and patient preferences (25). This recommendation was based on a systematic review comparing nonpharmacologic versus pharmacologic treatment of adult patients with MDD.

Gartlehner and colleagues reviewed randomized controlled trials published in English between 1990 and September 2015 and examined the comparative benefits and harms of antidepressants, psychotherapy, complementary and alternative medicine, and exercise for treatment of MDD. On the basis of moderate-quality evidence indicating equivalent benefit of pharmacotherapy and CBT and limited evidentiary basis for other interventions, the authors recommended offering patients with mild to

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Table 3. **Second-Generation (First-Line) Antidepressants**

Drug (Effective Dose Range)	*Benefits*	*Adverse Effects*	*Notes*
SSRIs	Effective Well tolerated	Serotonergic (nausea, diarrhea, nervousness, insomnia, impaired sexual function, withdrawal syndrome, hyponatremia in elderly persons*)	Contraindicated with monoamine oxidase inhibitors Potential for drug–drug interactions Delicate risk–benefit calculus in pregnancy
Fluoxetine (20–80 mg)	Extensive clinical experience Long half-life mitigates risk for withdrawal symptoms when tapering	See class effects	Early adverse effects may be delayed due to long half-life and drug accumulation Strong CYP2D6 inhibitor (potential for drug–drug interactions)
Sertraline (50–200 mg)	Wide dosage range allows for small dose adjustments to balance efficacy and tolerability Relatively low placental transmission from maternal bloodstream during pregnancy; relatively low concentrations in breast milk	Slightly increased incidence of short-duration diarrhea during first few weeks of therapy	Preferred in women of childbearing age Decreased drug–drug interactions Dual mechanism of action: SSRI and dopamine reuptake inhibition
Paroxetine (20–50 mg)	Relatively low placental transmission from maternal bloodstream during pregnancy; relatively low concentrations in breast milk	Higher risk for withdrawal or discontinuation symptoms than other serotonergic antidepressants Higher risk for weight gain Potential higher risk for teratogenic effects	Strong CYP2D6 inhibitor (potential for drug–drug interactions)
Citalopram (20–40 mg)	Few drug–drug interactions	May prolong QTc interval, particularly at higher doses	Not recommended in congenital long QTc syndromes and acute cardiac conditions (e.g., decompensated heart failure) Discontinue in patients with QTc interval >500 ms Doses >20 mg/d not recommended in elderly persons or in hepatic impairment
Escitalopram (10–20 mg)	Few drug–drug interactions	More modest effect on QTc interval at standard dosage range than citalopram	Narrow dosage range precludes small dose adjustments to balance drug efficacy and tolerability
SNRIs	Effective Dual mechanism of action May treat comorbid pain conditions	Noradrenergic (hypertension, dry mouth, constipation, insomnia) and serotonergic (nausea, diarrhea, nervousness, insomnia, impaired sexual function, withdrawal syndrome, hyponatremia in elderly persons*)	Not shown to be more or less efficacious than SSRIs
Venlafaxine (75–350 mg)	Wide dosage range allows for small dose adjustments to balance efficacy and tolerability	Slightly increased incidence of nausea and vomiting compared with other serotonergic antidepressants Higher risk for withdrawal symptoms than other serotonergic antidepressants SNRI most associated with hypertension, particularly at doses >300 mg/d	May increase blood pressure May reduce neuropathic pain
Desvenlafaxine (50–100 mg)	Few drug–drug interactions	See class effects	Nonscored tablets may make tapering more difficult May reduce neuropathic pain

Continued on following page

Table 3.–**Continued**

Drug (Effective Dose Range)	*Benefits*	*Adverse Effects*	*Notes*
Duloxetine (60–120 mg)	May be effective for comorbid pain at doses ≥60 mg/d†	See class effects	Cigarette smoking reduces plasma levels of duloxetine May reduce neuropathic pain
Levomilnacipran (40–120 mg)	–	See class effects	Not FDA-approved for treatment of anxiety disorders Expensive; no generic formulation is available
Other antidepressants			
Bupropion XR (300–450 mg) (atypical antidepressant)	Weight neutral Minimal to no sexual adverse effects Minimal withdrawal symptoms Approved for smoking cessation	May lower seizure threshold, particularly at higher doses May cause headache or classic noradrenergic adverse effects (e.g., dry mouth, sweating, constipation)	Strong CYP2D6 inhibitor (potential for drug–drug interactions) Relatively contraindicated in patients with personal history of seizures, family history of seizures, significant head trauma, or eating disorders Use with caution with other drugs that may lower seizure threshold and in patients with impaired hepatic function or anorexia/bulimia Do not use in patients with moderate to severe anxiety
Mirtazapine (15–45 mg) (atypical antidepressant)	May have faster onset of action than SSRIs‡ Minimal sexual adverse effects Minimal withdrawal symptoms	Increased appetite and somnolence (both may be advantageous in patients with reduced appetite and insomnia as symptoms of depression) Higher risk for weight gain	Use with caution in patients with renal impairment Concomitant benzodiazepines and alcohol should be avoided due to risk for oversedation
Vilazodone (10–40 mg) (serotonin partial agonist and reuptake inhibitor)	May have lower risk for sexual adverse effects than other serotonergic antidepressants	No generic formulation is currently available Not FDA-approved for treatment of anxiety disorders	Pharmacologically, functions similarly to a serotonin reuptake inhibitor combined with buspirone Expensive; no generic formulation is available
Vortioxetine (10–20 mg) (serotonin reuptake inhibitor and serotonin modulator)	May have lower risk for sexual adverse effects than other serotonergic antidepressants Long half-life may mitigate risk for withdrawal symptoms when tapering	High rates of nausea despite 5-HT_3 receptor antagonism	Not FDA-approved for treatment of anxiety disorders Controversial association with improvements in cognition Expensive; no generic formulation is available Narrow dosage range precludes small dose adjustments to balance drug efficacy and tolerability

CYP2D6 = cytochrome P450 2D6; FDA = U.S. Food and Drug Administration; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; XR = extended release.

** Wright SK, Schroeter S. Hyponatremia as a complication of selective serotonin reuptake inhibitors. J Am Acad Nurse Pract. 2008;20:47-51. [PMID: 18184165] doi:10.1111/j.1745-7599.2007.00280.x*

† Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hosp Psychiatry. 2009;31:206-19. [PMID: 19410099] doi:10.1016/j.genhosppsych.2008.12.006

‡ Qaseem A, Snow V, Denberg TD, et al; Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;149:725-33. [PMID: 19017591]

severe MDD either CBT or second-generation antidepressants as first-line treatment (24).

How should clinicians select an antidepressant?

Clinicians face a wide array of antidepressant drug options (**Table 3**). Antidepressants should be considered with intent to decrease the severity and duration of current depressive episodes and the probability of recurrent episodes. Treatment is typically initiated with a second-generation antidepressant (selective serotonin reuptake inhibitor [SSRI]; serotonin–norepinephrine reuptake inhibitor [SNRI]; or atypical antidepressant, such as

48. Carvalho AF, Sharma MS, Brunoni AR, et al. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom. 2016;85:270-88. [PMID: 27508501]

Table 4. **Follow-up for Depression***

Depression Severity	*Suggested Follow-up*
Minor	Watchful waiting; reevaluate in 4–8 wk
Mild (PHQ-9 score of 10–14)	Contact by telephone or in person monthly, regardless of whether antidepressants are prescribed
Moderate (PHQ-9 score of 15–19)	Contact by telephone or in person every 2–4 wk
Severe (PHQ-9 score ≥20)	Contact by telephone or in person every 2–4 wk until PHQ-9 score improves by ≥5 points
No active treatment, receiving ongoing stable antidepressants, or receiving counseling	Contact by telephone or in person every 2–3 mo after remission

PHQ-9 = Patient Health Questionnaire 9.
** Adapted from MacArthur Initiative on Depression & Primary Care. Depression Management Tool Kit. John D. and Catherine T. MacArthur Foundation; 2009.*

49. Anglin R, Yuan Y, Moayyedi P, et al. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. Am J Gastroenterol. 2014;109:811-9. [PMID: 24777151]
50. Targownik LE, Bolton JM, Metge CJ, et al. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol. 2009;104:1475-82. [PMID: 19491861]
51. Ziegelstein RC, Meuchel J, Kim TJ, et al. Selective serotonin reuptake inhibitor use by patients with acute coronary syndromes. Am J Med. 2007;120:525-30. [PMID: 17524755]
52. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: challenges and strategies. Neuropsychiatr Dis Treat. 2020;16:221-34. [PMID: 32021216]
53. Ren J, Li H, Palaniyappan L, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2014;51:181-9. [PMID: 24556538]
54. Kim J, Farchione T, Potter A, et al. Esketamine for treatment-resistant depression–first FDA-approved antidepressant in a new class. N Engl J Med. 2019;381:1-4. [PMID: 31116916]
55. Thachil AF, Mohan R, Bhugra D. The evidence base of complementary and alternative therapies in depression. J Affect Disord. 2007;97:23-35. [PMID: 16926053]

mirtazapine or bupropion). These medications have roughly equal efficacy and should decrease the severity and duration of a depressive episode, with the goal of restoring overall baseline function. Newer agents, such as vilazodone, vortioxetine, and levomilnacipran, may be cost-prohibitive because no generic formulation is currently available, and the lack of broad experience with them makes it unclear where they fit in the treatment algorithm. First-generation and non–first-line antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) may offer similar or greater effectiveness, but with less receptor specificity, a broader range of adverse effects, and more potential for toxicity (31).

Cipriani and colleagues conducted a network meta-analysis of 522 clinical trials involving 21 antidepressants (including SSRIs, SNRIs, TCAs, bupropion, mirtazapine, and newer antidepressants) in the treatment of adults with MDD. All antidepressants were found to be more efficacious than placebo, with limited differences in efficacy observed among them (32).

Drug selection should involve a discussion between the clinician and the patient. Factors to consider include tolerability, safety, evidence of effectiveness in the patient or a first-degree relative, age, potential for drug–drug interactions, presence of comorbid medical conditions, and cost.

How should clinicians monitor response to drug therapy?

Treatment of depression requires at least 6–9 months of close follow-up (**Table 4**). The first several weeks of drug therapy are often the most challenging. The pessimism and hopelessness intrinsic to depression and the relatively rapid onset of adverse effects can lead to nonadherence: 28% of depressed primary care patients stop taking their medication in the first month, and 44% stop within 3 months (33). It is essential to educate patients preemptively about adverse effects they might have with a specific medication.

Clinicians should see patients within 1–2 weeks of starting therapy to ask about acceptance of medication, reinforce educational messages, assess adherence, reassess danger to self or others, monitor emergence of mania, and address adverse events. Addressing specific adverse effects is critical to maintaining adherence until patients respond. Close follow-up by a nonphysician provider, such as a registered nurse or a licensed clinical social worker, is a key component of the collaborative care model of integrated psychiatric care in primary care settings (34). In addition, antidepressants may be associated

with increased risk for suicide in children, adolescents, and young adults.

A meta-analysis of 2741 patients aged 6–18 years showed an increased relative risk for self-harm or suicide-related events in patients treated with newer-generation antidepressants (SSRIs, venlafaxine, and mirtazapine) compared with those given placebo (4.8% vs. 3.0%; P = *0.01; number needed to treat for harm, 55). Because actual suicide is rare in such studies, the increase in risk for suicide rather than for suicidal behaviors can only be inferred (35*).

The U.S. Food and Drug Administration (FDA) has issued a Public Health Advisory recommending close monitoring of all patients treated with antidepressants, particularly in the first few months. A warning statement about a possible increased risk for suicide is included on the FDA patient information sheets for first-line antidepressants. Clinicians should ask about agitation, irritability, or unusual changes in behavior. Adults younger than 25 years have an increased risk for suicidal behavior with antidepressant treatment compared with placebo (odds ratio, 2.3) (36). The FDA recommends weekly follow-up of these patients for the first month, biweekly follow-up for the next month, and monthly follow-up thereafter. Of note, after these FDA recommendations were published, antidepressant use decreased and suicide attempts in young persons showed an accompanying increase (37).

Use of a standardized depression assessment tool, such as the PHQ-9, provides an objective measure of symptom change. If response to medication is inadequate after 6–8 weeks, treatment should be modified. Recurrence of depression after a first episode is common. Clinicians should educate patients and their families to self-assess for symptoms and risk for recurrent episodes. Surveillance for recurrence or relapse should continue indefinitely.

The goal of treatment is complete remission of symptoms and return to normal functioning. For the first episode, antidepressant treatment may require 1 to several months to achieve remission and should be continued for an additional 4–9 months to reduce risk for relapse. Some clinicians advocate treatment for at least 1 year to maintain remission for a full annual cycle of holidays and anniversaries, although this recommendation is not strictly evidence-based. For multiple episodes of depression, even longer therapy may be beneficial (29). For older patients (those aged >70 years) with major depression who respond to an SSRI, clinicians should consider treating for 2 years to prevent recurrence (38).

When should clinicians consider modifying treatment because of a suboptimal response to an antidepressant?

Many patients starting antidepressant therapy do not achieve complete remission, so a change in treatment plan is often necessary.

*STAR*D (Sequenced Treatment Alternatives to Relieve Depression) randomly assigned patients to 1 of several treatment sequences, all starting with 12 weeks of citalopram. The study showed that 30% of patients achieved complete remission after 12 weeks. Of those who did not improve with citalopram, about 25% responded to an alternative agent with a different mechanism of action (sertraline, venlafaxine, or bupropion), and another one third responded to augmentation with bupropion (39*).

For a partial response to an antidepressant (<50% symptomatic improvement) after 1 month of treatment, the dose can be increased by 50%–100% before considering switching medications or augmenting with a

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63. Gartlehner G, Gaynes BN, Amick HR, et al. Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatments for major depression: an evidence report for a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;164:331-41. [PMID: 26857743].
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second agent. When a partial response persists, the clinician can refer the patient for psychotherapy; change antidepressants; or augment treatment with bupropion, mirtazapine, or a nontraditional agent.

Compared with withdrawing one drug and starting another, drug augmentation offers faster effects, potential for synergistic or complementary effects, and avoidance of withdrawal symptoms when the first agent is stopped. However, drug interactions and adverse effects can increase with a more complex regimen.

Adding bupropion to an SSRI or venlafaxine may enhance response or treat adverse effects in many patients (40). Response rates are similar when mirtazapine is added to SSRI treatment (41). Combinations of MAOIs and either SSRIs or TCAs are strictly contraindicated due to increased risk for serotonin syndrome (with confusion, nausea, autonomic instability, and hyperreflexia). Adding an antipsychotic medication to an SSRI may benefit some patients but should be considered only by providers who are comfortable monitoring for possible extrapyramidal symptoms and metabolic derangements, such as diabetes and dyslipidemia (42). The second-generation antipsychotics extended-release quetiapine, aripiprazole, and brexpiprazole have FDA indications for augmentation in major depression. L-methylfolate is a prescription medical food approved for adjunctive use in major depression. A Cochrane review found that evidence was lacking to support a role for omega-3 fatty acids in the treatment of depression in adults, whereas yoga, self-help books, exercise, relaxation therapy, and acupuncture seem useful (43, 44). Light therapy has been shown to produce benefits similar to those of fluoxetine in nonseasonal depression (45), although this finding requires replication in larger studies to routinely recommend light therapy as initial or adjunctive treatment of MDD.

Lam and colleagues compared daily light treatment (10 000 lux for 30 minutes) versus fluoxetine versus combination treatment in adults with nonseasonal MDD for 8 weeks. Monotherapy light treatment was as effective as fluoxetine and significantly better than placebo (45).

What are common adverse effects of antidepressants, and how should clinicians manage them?

Specific types of adverse effects are more common with particular drugs and should guide medication choice (**Table 3**). Sexual adverse effects of SSRIs include decreased libido or interest, anorgasmia, and delayed ejaculation. To address these, clinicians should consider pretreatment counseling or switching to bupropion or mirtazapine, both of which have lower risk for sexual adverse effects. Sildenafil may also help SSRI-associated erectile dysfunction in patients who have no contraindications (46). Bupropion is associated with modest weight loss and may be suitable for depressed patients with hyperphagia. By contrast, mirtazapine and paroxetine have been associated with modest weight gain with maintenance treatment (averaging 2–3 kg), whereas other SSRIs and SNRIs have not been consistently associated with weight gain (47). Agitation or excessive activation, most commonly with fluoxetine, warrants switching to another SSRI and considering mixed mania. Adding mirtazapine, trazodone, or a sedative–hypnotic may reduce insomnia early in the treatment course. During SSRI initiation, clinicians may also provide a short course of benzodiazepines to treat prominent anxiety symptoms or severe distress associated with major depression. We suggest a low dose and short course of a long-acting benzodiazepine. Because SSRIs can exacerbate

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66. Fortney JC, Pyne JM, Edlund MJ, et al. A randomized trial of telemedicine-based collaborative care for depression. J Gen Intern Med. 2007;22:1086-93. [PMID: 17492326]

anxiety symptoms early in treatment, they can be started at 50% of the minimum therapeutic dose and then titrated to the minimum therapeutic dose after 1 week as tolerated. Serotonergic antidepressants (for example, SSRIs and SNRIs), especially paroxetine and venlafaxine, are associated with a withdrawal syndrome and usually require a gradual taper over several weeks to mitigate risk for these symptoms. SSRIs have also been associated with upper gastrointestinal bleeds, hyponatremia in elderly persons, and osteoporosis (48).

A recent meta-analysis found that SSRIs were associated with increased risk for upper gastrointestinal bleeding. Risk was further increased with concomitant use of nonsteroidal anti-inflammatory drugs (49) but was significantly attenuated by co-treatment with a proton-pump inhibitor (50). Conversely, Ziegelstein and colleagues showed that SSRI use in patients with coronary artery disease led to decreased ischemia due to heart failure (51). These effects are postulated to be secondary to the effect of SSRIs on platelets.

When should clinicians consult a psychiatrist for help in managing drug therapy?

Referral to a psychiatrist may be necessary for patients who do not respond to agents familiar to the primary care provider, patients who have repeated failures, or patients with adverse effects that are difficult to manage. The threshold for referral should be lower for more severely impaired patients. The Agency for Healthcare Research and Quality recommends a psychiatric consultation for severe symptoms, heightened suicide risk, comorbid psychiatric or substance abuse problems, or lack of response to appropriate treatment. Major depression with psychosis, which requires the addition of an antipsychotic medication, is best managed by a psychiatrist.

Many treatment options are available for treatment-resistant depression, administered under the supervision of a psychiatrist. Electroconvulsive therapy (ECT) should be considered for patients with treatment-resistant depression, particularly those with concurrent psychotic features, catatonia, and/or suicidality. ECT is the most effective therapy for treatment-resistant depression (52) but requires general anesthesia and careful consideration of medical comorbidities. Transcranial magnetic stimulation is a newer, potentially safer, and better-tolerated option than ECT, but it is not as effective for treatment-resistant depression (53). Esketamine, an analogue of ketamine, is a newer therapy that is FDA-approved for treatment-resistant depression in conjunction with an oral antidepressant. Esketamine is administered intranasally and has a rapid onset of action (54).

When should clinicians consider hospitalizing depressed patients?

The decision to hospitalize is usually reserved for patients who experience significant suicidal ideation or intent without safeguards in the family environment, express intent to hurt others, or are unable to care for themselves (for example, not eating). Other indications include a requirement for close observation (to assess self-care and adherence), detoxification or substance abuse treatment, initiation of ECT, or dysfunctional family systems that worsen the depressive disorder or interfere with treatment. When a patient's life is in jeopardy, hospitalization against their wishes is necessary. The legal requirements for involuntary detainment to treat mental illness are established by each state and local region.

What should clinicians advise patients about complementary and alternative treatments?

Evidence indicates varying degrees of success with complementary treatments for depression. Examples include L-methylfolate, omega-3 fatty acids, *S*-adenosyl-L-methionine, St. John's wort (*Hypericum perforatum*), and 5-hydroxytryptophan (5-HTP), as well as regular physical exercise and acupuncture (55). Use of complementary medicinal treatments should be monitored for potential drug–drug interactions. Use of 5-HTP or St. John's wort with an SSRI, for example, may increase risk for serotonin-related adverse effects or serotonin syndrome.

If a patient relapses after cessation of treatment, should clinicians resume previously effective therapy or select a new therapy?

If a patient has depression recurrence, prior treatment should be resumed unless it was terminated secondary to adverse effects (26). Lifetime therapy may be required for patients with 3 or more depressive episodes or with a first recurrence and risk factors for more recurrences (family history of bipolar disorder, recurrence after <1 year, onset in adolescence, severe depression, suicide attempt, and sudden onset of symptoms) (26).

How should clinicians advise women receiving drug therapy for depression who are or who wish to become pregnant?

Several epidemiologic studies have assessed the effects of antidepressants (primarily SSRIs) on maternal and fetal outcomes in pregnancy. Overall, the teratogenic potential of SSRIs is considered low (56). Nonetheless, 2 epidemiologic studies showed an association between paroxetine in early pregnancy and newborn cardiac defects, prompting the FDA in late 2005 to order a change in labeling for this agent. In 2006, the FDA issued a warning and a subsequent public health advisory

about SSRI use during pregnancy. This was based on a case–control study that showed a 6-fold greater incidence of persistent pulmonary hypertension (PPHN) in infants whose mothers received an SSRI after the 20th week of gestation. Absolute risk for infant PPHN was low (about 6–12 cases per 1000 exposed mothers) (57). Before FDA pregnancy categories were discontinued in 2014, paroxetine was the only SSRI categorized as class D (indicative of positive evidence of human fetal risk), whereas other SSRIs were categorized as class C. Subsequent studies have shown considerably more modest risk (58). In 2011, the FDA updated its advisory and concluded that it was unclear whether SSRIs cause PPHN.

In a nested cohort study in nearly 4 million pregnant Medicaid recipients from 2000–2010 in 46 states, the adjusted odds ratio for primary PPHN with SSRIs was 1.28 (95% CI, 1.01–1.64) (55).

In a recent meta-analysis of the relationship that involved nearly 2 million participants included in the follow-up, the authors found no association between first-trimester SSRI use and newborn heart defects (59).

When taken by the pregnant mother, SSRIs and SNRIs may also confer a risk for neonatal adaptation syndrome, where the newborn experiences acute effects of antidepressant withdrawal. Symptoms generally occur within 1 week of birth; may include irritability and/or excessive crying, poor feeding, and tremor; and are usually self-limited and short-lived (60).

It should be noted that stopping antidepressants during pregnancy may increase risk for depression relapse. Antenatal depression is associated with increased risk for adverse neonatal outcomes, including fetal growth restriction, premature delivery, and low birthweight (61). These are considered high-risk pregnancies and should be comanaged by a psychiatrist and an obstetrician.

In 201 pregnant women with a history of major depression before pregnancy, relapse was more common in those who stopped their medication than in those who continued (68% vs. 26%; hazard ratio, 5.0; P < 0.001) (62).

In summary, the risks of ongoing antidepressant therapy during pregnancy must be weighed against the risks of treatment cessation. Clinicians should help patients make an informed decision and should monitor them for signs of postpartum depression in the first 4–6 weeks after delivery.

Treatment... Primary care physicians play an important role in treating affective disorders. Depression is highly treatable—clinicians who are familiar with 2 SSRIs (such as citalopram and sertraline), an SNRI (such as extended-release venlafaxine), and extended-release bupropion are well equipped to treat most cases. However, they should not hesitate to refer patients to a psychiatrist for evaluation, comanagement, or team-based collaborative care. Familiarity with local psychotherapy options and options for addressing common adverse effects is also helpful.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend with regard to screening for and management of depression?

In 2016, the U.S. Preventive Services Task Force reiterated its recommendation for universal screening in adult patients, provided that adequate resources are in place for follow-up and treatment. No screening intervals were proposed (11). The American College of Physicians updated its guidelines for treatment of MDD in 2016 (63), recommending initiation of CBT or second-generation antidepressants after a thorough discussion of risks, treatment benefits and costs, accessibility, and patient preferences. Initial treatment solely with depression-focused psychotherapy is recommended for persons with mild to moderate MDD and in women who are pregnant, wish to become pregnant, or are breastfeeding. Regardless of the initial treatment method, close follow-up and reassessment are critical to determining whether treatments are effective and outcomes are achieved.

How can primary care practices improve depression care?

Depression is a chronic illness that must be tracked and monitored over time. Primary care systems must invest in systematic practice change to improve depression care. Fortunately, well-studied integrated behavioral and primary care service models can result in dramatic improvements in

depression response and remission while paying for themselves (64). A 2012 Cochrane analysis reviewed nearly 80 randomized controlled trials across diverse practice settings of collaborative care (a particular form of "integrated care"), finding consistent evidence to improve anxiety and depressive disorder outcomes (65).

Collaborative care has been widely embraced by the psychiatric community as a method to deliver evidence-based mental health therapies to a broader portion of the population, thus improving access to treatments and quality of care. Collaborative care involves a team of clinicians, including a primary care physician, a psychiatric consultant, and a care manager, all caring for a group of patients with depression or anxiety disorders in primary care. The collaborative care team tracks this population over time, paying attention to measurement-based outcomes (such as the PHQ-9) and progressively intensifying engagement, outreach, and treatment until the specified outcomes are achieved. The collaborative care model is based on the principles of the chronic care model (64) and easily fits into evolving models of primary care practice reform, such as the patient-centered medical home. Recent advances in workforce training and reimbursement, including the approval of new CPT (Current Procedural Terminology) coding for collaborative care programs, have lowered significant barriers to more widespread adoption of this approach. Collocation of behavioral health services in primary care practices has not been shown to consistently improve outcomes or reduce costs across patient populations but can be a helpful step toward implementing collaborative care models. Nevertheless, collocation is not a requirement of collaborative care, which has been shown to be effective in improving outcomes and reducing costs even when practiced from remote locations via telemedicine (66).

In the Clinic
Tool Kit

Depression

Patient Information

https://medlineplus.gov/depression.html

https://medlineplus.gov/languages/depression.html

Information and handouts in English and other languages from the National Institutes of Health's MedlinePlus.

www.nimh.nih.gov/health/publications/depression/index.shtml

Information and handouts from the National Institute of Mental Health.

www.psychiatry.org/patients-families/depression/what-is-depression

Information from the American Psychiatric Association.

Information for Health Professionals

https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

2010 practice guideline for the treatment of patients with major depressive disorder from the American Psychiatric Association.

www.acpjournals.org/doi/10.7326/M15-2570

2016 clinical practice guideline on nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder from the American College of Physicians.

https://jamanetwork.com/journals/jama/fullarticle/2484345

2016 recommendation statement on screening for depression in adults from the U.S. Preventive Services Task Force.

WHAT YOU SHOULD KNOW ABOUT DEPRESSION

What Is Depression?

Depression is a common mood disorder that causes feelings of sadness or emptiness. It may make it hard to enjoy regular activities and can cause problems in your life. It is different from feeling down for a few days because it does not go away. Untreated depression can last for months or years and may worsen other medical problems.

What Causes It?

Depression affects 5%–10% of the U.S. population, and everyone is at risk. People with chronic medical conditions, a personal or family history of depression, or lower socioeconomic status have a higher risk for depression during their lifetime.

Having some of these symptoms every day for at least 2 weeks may indicate depression:

- Sadness
- Feeling less interested in things you used to enjoy
- Changes in appetite
- Unintentional weight loss or gain
- Sleeping too much or too little
- Feeling tired
- Feeling guilty or worthless
- Trouble concentrating
- Thoughts of death or suicide

How Is It Diagnosed?

- You may be asked to complete a short survey that asks questions about your mood, your behavior, and how often you experience feelings of depression.
- Your doctor will review the results of the survey with you and ask follow-up questions about your feelings and if you are having suicidal thoughts. He or she may also ask if you have access to firearms.
- Your doctor will ask about your medical history, including any history of mania/hypomania, anxiety, substance use disorder, and psychosis. You will also have a physical examination.
- Your doctor will review medicines you are taking and ask about other substances you use.

How Is It Treated?

- There are many available treatments that work alone or in combination. You and your doctor will work together to identify the best plan for you. It may take 1–2 months before you start to feel better on whatever treatment you select.
- You may be referred for psychotherapy, which involves talking with a therapist to help you change your thoughts and behaviors and

improve your ability to cope. This can be as effective as medication for mild or moderate depression and may better prevent relapse.

- You may be prescribed an antidepressant medicine. The type will depend on how severe your depression is and your symptoms.
- It is important to know the side effects of the medication and to notify your doctor before stopping any medication because of side effects. Side effects are usually most severe in the first few weeks and improve over time. They differ between antidepressants, so it is easy to switch medications if you are having trouble.
- If you do not feel better after 2 months of treatment, talk to your doctor and adjust the plan.
- Treatment should last for at least 4–9 months to prevent relapse.
- See your doctor for regular follow-up and ongoing monitoring during treatment.
- Self-care strategies like yoga, self-help books, exercise, relaxation therapy, acupuncture, and light therapy may also help your depression.
- Don't be afraid to ask for help. If you feel you may harm yourself or need help, call 911 or go to the emergency department right away.

Questions for My Doctor

- How do I know if I'm depressed or just sad?
- Do I need medicine to treat my depression?
- What are the side effects of the medication?
- What should I do if I have side effects?
- How long does it take for the medication to work?
- Do alternative therapies help with depression?
- Can you help me find a therapist who takes my insurance?
- Should I see a psychiatrist?
- Can I take antidepressants if I am pregnant or planning to become pregnant?
- What should I do if treatment does not make me feel better?

For More Information

ACP[SM]
American College of Physicians
Leading Internal Medicine, Improving Lives

National Institute of Mental Health
www.nimh.nih.gov/health/publications/depression/index.shtml

MedlinePlus
https://medlineplus.gov/depression.html

Patient Information