UpToDate®
Official reprint from UpToDate®
www.uptodate.com © 2024 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Major depressive disorder in adults: Initial treatment with antidepressants

AUTHOR: A John Rush, MD
SECTION EDITORS: Peter P Roy-Byrne, MD, Robert McCarron, DO
DEPUTY EDITORS: Sara Swenson, MD, David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2024.**
This topic last updated: **Sep 19, 2024.**

INTRODUCTION

Major depressive disorder (MDD, or unipolar major depression) is highly prevalent and a significant source of disability. Community surveys in 14 countries have estimated that the lifetime prevalence of depressive disorders is 12 percent [1]. In patients with other medical illnesses, such as diabetes or coronary heart disease, the estimated prevalence of MDD is 10 to 20 percent [2]. In the United States, MDD ranks second among all diseases and injuries as a cause of disability [3]. According to the World Health Organization, it is the 11th greatest cause of disability and mortality in the world [4].

MDD is undertreated. As an example, community surveys examined how many individuals with MDD in the past 12 months received minimally adequate treatment, defined as at least eight psychotherapy visits or at least four pharmacotherapy visits [5]. Among individuals with MDD in higher income countries, only 22 percent received minimally adequate treatment; in lower income countries, it was only 4 percent.

MDD is also highly recurrent. Following recovery from one episode, the estimated rate of recurrence over two years is greater than 40 percent; after two episodes, the risk of recurrence within five years is approximately 75 percent [6].

This topic reviews the use of antidepressants for the initial management of MDD, including considerations for choosing an antidepressant medication and a starting dose and monitoring outcomes to personalize dose titration and detect and minimize side effects. Other aspects of

treating depression are discussed separately, including how to choose among pharmacotherapy, psychotherapy, and/or nonpharmacologic options; treatment of resistant depression; and continuation and maintenance treatment of MDD.

- (See "Major depressive disorder in adults: Approach to initial management".)
- (See "Major depressive disorder in adults: Treatment with supplemental interventions".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Major depressive disorder in adults: Continuation and maintenance treatment".)
- (Related Pathway(s): Unipolar major depression: Initial pharmacologic therapy in adults.)

DEFINITIONS

- **Major depressive disorder** – MDD is diagnosed in patients with a history of at least one major depressive episode (table 1) and no history of mania (table 2) or hypomania (table 3) [7]. In this topic, the term "major depression" refers to MDD.
- **Major depressive episode** – A major depressive episode is a period lasting at least two consecutive weeks, with five or more of the following symptoms: depressed mood, anhedonia, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide. At least one symptom must be depressed mood or anhedonia, and the symptoms must cause significant distress or functional impairment. A major depressive episode can occur in major depressive or bipolar disorders as well as other psychiatric disorders.
- **Phases of depression** – Trials of interventions to treat depression often use specific depression rating scales to rate symptom severity and describe clinical outcomes. The following commonly used terms delineate phases of treatment (figure 1) [8]. Although these definitions are useful for conceptualizing the illness course of depression and evaluating treatment interventions, they are not standardized. In clinical practice, the terms "relapse" and "recurrence" are often used interchangeably, as are "remission" and "recovery" [8].
  - **Response** – Response is the reduction of depression symptoms by a clinically meaningful, specified amount. Response is usually defined as an improvement in

symptom score of ≥50 percent that is still above the threshold for remission [9,10].

- **Partial response** – Partial response is defined as an improvement in symptom score of >30 but <50 percent. However, definitions used in individual studies differ [9,10].

- **Nonresponse (no meaningful benefit)** – A nonresponse to depression treatment is usually defined as a change in symptom score of ≤30 percent.

- **Remission** – Remission is the stable reduction of symptoms below the threshold (or specific cutoff) for diagnosis. Studies using the nine-item Patient Health Questionnaire (PHQ-9) often define remission as a score of <5 (table 4). The Montgomery-Asberg Depression Rating Scale (figure 2A-C) often defines remission as a score ≤9.

- **Recovery** – Recovery occurs when symptom remission has been sustained for 8 to 24 weeks [11-15].

- **Relapse** – Relapse is the return of depressive symptoms prior to the time of recovery.

- **Recurrence** – Recurrence is the onset of a new episode of major depression after recovery from a prior episode.

- **Depression severity** – The severity of depression is determined by the combination of functional impairment and the number, frequency, intensity, and duration of the individual's symptoms. (See "Major depressive disorder in adults: Approach to initial management", section on 'Determination of severity'.)

  We use the self-report PHQ-9 and other features of the patient's symptoms to define the severity of a major depressive episode (table 5). The PHQ-9 classifies episodes as mild (scores of 5 to 9), moderate (10 to 14), moderately severe (15 to 19), and severe (20 or higher) (table 4). Alternative validated self-report scales for evaluating depression symptoms include the Quick Inventory of Depressive Symptomatology – Self-Report and the Clinically Useful Depression Outcome Scale [16]. Using symptom scales to monitor response to treatment and categorize symptom severity is discussed separately.

GOALS AND INDICATIONS FOR PHARMACOTHERAPY

- **Indications** – We include antidepressants as part of the management plan for patients with moderate to severe MDD. Other indications include some individuals with mild depression who strongly prefer treatment with medications, have lack access to

psychotherapy, and/or have symptoms that have not responded to nonpharmacologic management. This is discussed in detail separately. (See "Major depressive disorder in adults: Approach to initial management", section on 'Choosing a treatment regimen for patients with major depression'.)

- **Goals of treatment** – The goals of initial treatment for depression are to restore baseline functioning, induce symptom remission, and prevent relapse [17-20]. Relapse occurs less frequently in patients whose symptoms remit with initial management, compared with those whose symptoms respond but do not remit [21].

CLASSES OF ANTIDEPRESSANTS

Second-generation antidepressants include those in the following classes (table 6):

- Selective serotonin reuptake inhibitors (see "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects")
- Serotonin-norepinephrine reuptake inhibitors (see "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects")
- Atypical antidepressants (see "Atypical antidepressants: Pharmacology, administration, and side effects")
- Serotonin modulators (see "Serotonin modulators: Pharmacology, administration, and side effects")

Older, first-generation antidepressants (table 6 and table 7) include:

- Tricyclic antidepressants (see "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects")
- Monoamine oxidase inhibitors (see "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects")

SELECTING AN ANTIDEPRESSANT

Patients with mild to moderate depression — Mild to moderate depression is defined by nine-item Patient Health Questionnaire (PHQ-9) symptom scores of 5 to 9 (mild) and 10 to 19 (moderate to moderately severe) (table 4).

Treatment approach — For individuals with mild to moderate major depression who opt for antidepressants, we consider various factors other than efficacy alone because clear differences

in efficacy between antidepressants have not been found. These factors include the patient's history of prior antidepressant use, specific depressive symptoms, preferences for avoiding certain antidepressant side effects, other current medications, and psychiatric and medical comorbidities (table 7) [17,22].

In most patients, we use a selective serotonin reuptake inhibitor (SSRI), such as escitalopram or sertraline, unless there is a compelling reason to avoid SSRIs or select a specific agent from a different class. SSRIs generally offer an optimal balance of efficacy and tolerability. (See 'General preference for SSRIs' below.)

Reasons to select a drug from a different class are shown in a table (table 8) and discussed in detail. (See 'Tailoring antidepressant selection' below.)

Reasonable first-line alternatives to SSRIs include other second-generation antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs); atypical antidepressants, such as mirtazapine or bupropion; and serotonin modulators (table 6). Concerns about safety, particularly in overdose, and higher rates of adverse effects limit the use of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors for initial treatment. (Related Pathway(s): Unipolar major depression: Initial pharmacologic therapy in adults.)

For patients with mild to moderate major depression, the efficacy of different antidepressants is generally comparable across and within classes [17,23-28]. Although some systematic reviews show minor differences in the efficacy, patient acceptance, and adverse effects of different antidepressants, these are generally not considered clinically meaningful [17,23,25,28,29]. Representative examples from the literature include:

- A 2018 network meta-analysis of 522 randomized trials evaluated 21 antidepressants in more than 100,000 patients and found only small differences in response rates and acceptability (measured by medication discontinuation) [24].
- A network meta-analysis of 119 randomized trials found comparable efficacy across 16 second-generation antidepressants [30].

Existing evidence suggests that different antidepressant agents show similar efficacy in preventing relapse and recurrence. (See "Major depressive disorder in adults: Continuation and maintenance treatment", section on 'Antidepressant medications'.)

The efficacy of antidepressants compared with other treatment options (eg, placebo, psychotherapy) is discussed separately. (See "Major depressive disorder in adults: Approach to

initial management", section on 'Moderate major depression' and "Major depressive disorder in adults: Approach to initial management", section on 'Antidepressant medications'.)

The utility of pharmacogenomics, machine learning tools, and electroencephalography-based models to guide antidepressant prescribing is being actively investigated; however, a clear role for these practices has not yet emerged [31-33]. The role of genetic factors in influencing an individual's response to antidepressants is discussed separately. (See "Unipolar depression: Genetics", section on 'Pharmacogenetics'.)

General preference for SSRIs — We suggest selective serotonin reuptake inhibitors (SSRIs) if other reasons to tailor antidepressant choice are not a priority (table 8). SSRIs are the most widely prescribed class of antidepressants, and their potential for overdose toxicity is low [34-37]. We typically use escitalopram or sertraline because they may offer small advantages in terms of efficacy and acceptability. Fluoxetine offers the advantage of a long half-life, which can minimize any side effects associated with intermittent adherence or discontinuation of the medication. Although paroxetine also demonstrates high efficacy and acceptability, we choose this agent less frequently due to its side effects of weight gain and higher rates of discontinuation symptoms [38]. Representative studies that support this approach include:

- A 2018 network meta-analysis of 522 trials and over 100,000 participants ranked antidepressants in terms of efficacy and acceptability. Antidepressants that ranked the highest for both efficacy and acceptability included the SSRIs escitalopram, sertraline, and paroxetine as well as the atypical agents mirtazapine and agomelatine (not available in the United States) [30].

- A second network meta-analysis of second-generation antidepressants found superior efficacy plus tolerability (dropout due to adverse effects) with escitalopram, mirtazapine, and agomelatine [39]. An earlier network meta-analysis of 10 second-generation antidepressants also reported a slightly higher rate of remission with escitalopram [40].

It is reasonable to select other SSRIs based on clinician familiarity, cost, or desire to avoid certain side effects (such as diarrhea with sertraline), particularly since the preponderance of the evidence suggests that few clinically meaningful differences exist between the SSRIs. (See 'Treatment approach' above.)

Tailoring antidepressant selection — Although we typically choose SSRIs when initiating antidepressant therapy for the initial treatment of individuals with mild to moderate depression, specific patient characteristics often inform the selection of a specific SSRI or of antidepressants from other classes.

Addressing specific symptoms — We often choose an antidepressant that can address a patient's specific symptoms or coexisting conditions (eg, pain, anxiety, and tobacco use). Approaches to common situations appear in a table (table 8) and are discussed as follows:

- **Anxiety symptoms** – Symptoms of anxiety (eg, ruminative thoughts, worrying, and agitation) are common in individuals with MDD. Moreover, up to 75 percent of individuals with MDD have a co-occurring anxiety disorder, such as panic disorder or generalized anxiety disorder [41].

  The SSRIs are still a reasonable first choice in individuals with anxiety symptoms. SSRIs are also preferred agents for the initial pharmacotherapy of anxiety disorders (see "Generalized anxiety disorder in adults: Management" and "Social anxiety disorder in adults: Treatment overview" and "Panic disorder in adults: Treatment overview"). We typically start with one-half the usual initial antidepressant dose to minimize the transient activation that occurs with SSRIs and SNRIs.

  We generally avoid the use of bupropion in patients with significant anxiety. Adding a low-dose anxiolytic, such as clonazepam (0.25 or 0.5 mg at bedtime), can also treat anxiety symptoms and may enhance antidepressant adherence, particularly during the early stages of treatment. The indications and general principles for using anxiolytics, as well as their efficacy, are discussed separately. (See "Unipolar depression in adults: Treatment with anxiolytics".)

  Most evidence suggests that second-generation antidepressant agents are comparable for treating anxiety symptoms. As an example, a systematic review of 11 randomized trials of over 2300 participants with MDD found that different classes of second-generation antidepressants (SSRIs, SNRIs, atypical antidepressants, and serotonin modulators) showed similar efficacy in treating anxiety symptoms [42]. In contrast, an earlier review of 10 randomized trials of individuals with major depression and anxiety found higher response rates with SSRIs than bupropion in the subset of patients with high levels of anxiety symptoms [43].

- **Insomnia** – Because sleep disturbance associated with depression often improves as depression abates, most antidepressants can decrease insomnia. However, some individuals with severe insomnia may benefit from a sedating antidepressant, such as mirtazapine. Trazodone is also sedating; however, at a therapeutic antidepressant dose (200 to 400 mg daily), its side effects of sedation, nausea, and orthostatic hypotension are difficult for many individuals to tolerate.

Although many antidepressants are associated with side effects of insomnia, this side effect is usually transient (during the initial two to four weeks of treatment). As an example, in a network meta-analysis of 163 studies of 21 antidepressants, 14 were associated with an increased risk of insomnia, compared with placebo [44]; those agents most associated with insomnia included reboxetine, vilazodone, desvenlafaxine, duloxetine, and bupropion (table 7). In contrast, fluvoxamine, trazodone, and mirtazapine had the highest risk of somnolence.

However, available evidence suggests that second-generation antidepressants are comparable in treating insomnia symptoms in individuals with major depression. As an example, a systematic review of six randomized trials with over 1000 participants did not find compelling evidence that one agent or medication class was superior for the treatment of insomnia [42]. Sleep disturbance generally improves with treatment of depression, and this may partly explain the comparable efficacy of antidepressants for treating insomnia. Additional information on managing insomnia is discussed separately. (See "Overview of the treatment of insomnia in adults" and "Pharmacotherapy for insomnia in adults".)

- **Chronic pain** – The SNRIs duloxetine and milnacipran and TCAs may reduce neuropathic pain and may be useful options in individuals with concomitant major depression and chronic neuropathic pain [45]. Treatment of chronic noncancer pain with antidepressants is discussed elsewhere. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Antidepressants'.)

- **Tobacco use** – Bupropion is effective for treating tobacco use disorder and can be useful for individuals with depression who also wish to stop smoking. (See "Pharmacotherapy for smoking cessation in adults", section on 'Bupropion'.)

Caution with certain comorbidities — In selecting an antidepressant, we consider coexisting medical conditions that can be exacerbated by certain antidepressant agents. Some antidepressants can exacerbate specific medical conditions, such hypertension and seizure disorder. Some of the most common medical conditions to consider include the following:

- **Hypertension** – We suggest avoiding venlafaxine in individuals with uncontrolled hypertension, especially the immediate-release formulation at higher doses. If a compelling reason exists to choose an SNRI, duloxetine or lower-dose venlafaxine can be used. Venlafaxine use in this context should be accompanied with careful blood pressure monitoring. (See 'Address side effects' below.)

Some studies have found a dose-dependent association between venlafaxine and blood pressure elevation in both normal and hypertensive individuals, and case reports exist of venlafaxine precipitating hypertensive crisis [46]. However, other studies have not confirmed this association [47]. The effects of venlafaxine on blood pressure are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

- **Seizure disorder** – We suggest avoiding bupropion in individuals with seizure disorder or increased risk of seizure. Second-generation antidepressants can lower the seizure threshold, and bupropion is specifically contraindicated in individuals with seizure disorder or increased risk of seizure (ie, current or prior anorexia nervosa/bulimia, abrupt discontinuation of alcohol or benzodiazepines). In a population-based registry study of over 10,000 individuals, exposure to antidepressant agents was associated with an increased risk of new-onset seizure (odds ratio [OR] 1.5, 95% CI 1.3-1.6) [48]. The increase in seizure risk was highest with bupropion (OR 2.23, 95% CI 1.58-3.16) but also seen with SSRIs, SNRIs, and mirtazapine. However, even with bupropion, the absolute risk of seizures is low (0.1 percent), with the incidence increasing to 0.4 percent at higher doses. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Side effects'.)

- **QTc prolongation** – Citalopram and escitalopram can cause dose-dependent corrected QT interval (QTc) prolongation that is dose related. We suggest avoiding citalopram in patients with congenital long QT syndrome and using caution when prescribing citalopram to those with other medical conditions and/or on medications that cause QT prolongation. We also suggest avoiding doses of escitalopram of 30 mg/day or higher in these patients. Clinical trials suggest that escitalopram at doses less than 30 mg/day does not cause clinically significant QTc prolongation. Cardiac adverse effects of SSRIs are discussed in detail elsewhere. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Cardiac'.)

- **Hyponatremia** – Antidepressants (SNRIs, TCAs, mirtazapine, and particularly the SSRIs) may be associated with the syndrome of inappropriate antidiuretic hormone secretion and hyponatremia, although the absolute risk of hyponatremia appears low. In patients at high risk of hyponatremia, clinicians may choose fluvoxamine or milnacipran since hyponatremia occurs less frequently with these medications [49]. The risk of SSRI- and SNRI-induced hyponatremia is discussed elsewhere. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Hyponatremia' and

"Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

- **Low bone density** – Some observational studies suggest an association between some classes of antidepressants (SSRIs and TCAs) and fragility fractures and/or bone loss. However, studies to date have not confirmed a causal relationship, and we do not recommend avoiding antidepressants in individuals with osteoporosis or osteopenia. This association is discussed elsewhere. (See "Drugs that affect bone metabolism", section on 'Antidepressants'.)

- **Pregnancy** – For females who are considering pregnancy in the next year, certain medications should be avoided because of potential risks or an inadequate record of safety. We typically avoid paroxetine in this setting because some observational studies suggest that its use may be associated with a small increased absolute risk of congenital heart defects. This is discussed elsewhere. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Choosing an antidepressant'.)

Avoiding specific side effects — Helping individuals with depression avoid important side effects can help guide the choice of a specific antidepressant agent. Although some patients with MDD are willing to tolerate side effects from a medication that improves their symptoms, others prioritize avoiding specific side effects. Minimizing side effects helps to ensure that patients can tolerate a therapeutic dose and will adhere to pharmacotherapy. Whereas some adverse effects (eg, gastrointestinal side effects) (table 7) are common with second-generation antidepressants, others differ in frequency between different antidepressants, as described below [50].

- **Weight gain** – For patients who prioritize not gaining weight, we suggest bupropion or fluoxetine. Bupropion may have a lower risk of weight gain than other antidepressants [51-53]. Because mirtazapine and paroxetine cause more weight gain than other antidepressants, we generally avoid using them in this subset of patients [25,28,52,54-56]. Escitalopram and duloxetine have also been associated with short-term (six-month) weight gain [53].

  Most antidepressants are associated with weight gain. As an example, in a population-based cohort of nearly 300,000 primary care patients in the United Kingdom, antidepressant use was associated with a modestly higher incidence of weight gain of ≥5 percent, compared with no antidepressant use (11.2 versus 8.1 per 100 person-years; adjusted relative risk 1.21; 95% CI 1.19-1.22) [54]. Similarly, a retrospective cohort of patients with depression who were treated with a variety of second-generation

antidepressants reported average weight gains at two-year follow-up that ranged from 1 to 7 kg [52].

Weight gain usually starts after the first four to six months of treatment, and the magnitude of weight gain is generally small [51]. In a cohort of 183,118 participants who were prescribed one of eight commonly used antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine), mean weight changes at six months ranged from -0.01 to 0.63 kg [53]. Escitalopram (mean weight difference 0.41 kg), paroxetine (0.37 kg), and duloxetine (0.34 kg) were associated with the greatest weight gain compared with sertraline, which served as the reference standard. By contrast, bupropion was associated with slight weight loss (mean weight difference -0.22 kg). Only escitalopram, paroxetine, and duloxetine were associated with a statistically significant risk of clinically meaningful weight gain, which was defined as ≥5 percent increase from baseline weight.

Additional information about weight change with SSRIs is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Weight change'.)

- **Weight loss** – Individuals with major depression who need to avoid weight loss can use mirtazapine and most other antidepressants. They should ideally avoid bupropion. In a meta-analysis of randomized trials and cohort studies, weight loss was associated with short-term treatment with bupropion, duloxetine, fluoxetine, and sertraline [57].

- **Somnolence** – The less-sedating antidepressants, such as bupropion, reboxetine, or vilazodone, may be useful for patients with prominent symptoms of hypersomnia or lack of energy [44]. For individuals wishing to minimize sedation, we generally do not use fluvoxamine, trazodone, mirtazapine, or TCAs, all of which can cause somnolence (table 7).

- **Sexual dysfunction** – We recommend bupropion or mirtazapine for individuals who prioritize avoiding sexual dysfunction. Vortioxetine and vilazodone are also options for these patients. Sexual dysfunction is common in individuals with depression, even those who are not taking antidepressants. Sexual dysfunction occurs in over 50 percent of individuals taking SSRIs and is also seen with SNRIs. Symptoms of sexual dysfunction from antidepressants include decreased libido, difficulty achieving orgasm, and erectile dysfunction. Moreover, sexual dysfunction can persist after cessation of SSRIs and SNRIs (post-SSRI sexual dysfunction) [58,59]. The management of SSRI-induced sexual

dysfunction is discussed elsewhere (algorithm 1). (See "Sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs): Clinical features and management".)

- **Gastrointestinal side effects** – Gastrointestinal side effects are common with SSRIs. Nausea and vomiting occur in over 20 percent of those taking SSRIs; however, these side effects are most pronounced with medication initiation and titration and often diminish or resolve after the first several weeks of treatment. Nausea also occurs more frequently with venlafaxine than with SSRIs (33 versus 22 percent). Diarrhea is slightly more common with sertraline than with venlafaxine, mirtazapine, bupropion, and other SSRIs but generally limited to the first week (16 versus 8 percent of patients).

  TCAs can also cause constipation and dyspepsia due to their anticholinergic properties. This is particularly common with the first-generation TCAs (eg, amitriptyline, imipramine).

Prior antidepressant use — Choosing an antidepressant is often based upon patient response to specific antidepressants during prior depressive episodes or family history of response to antidepressants [60]. However, robust evidence does not exist to support this practice.

Patients with severe major depression — Severe major depression is characterized by seven to nine depressive symptoms (table 1) that occur nearly every day, as indicated by a score ≥20 points on the PHQ-9 (table 4). Individuals with severe major depression often report suicidal ideation and behavior, demonstrate obvious impairment of functioning, and are more likely to develop complications such as psychotic or catatonic features. Management of patients with severe major depression can require hospitalization and should ideally include referral to a psychiatrist [17].

We suggest combination treatment with psychotherapy and medication for individuals with severe major depression. Reasonable alternatives to combination treatment include medication alone or electroconvulsive therapy. Selecting a treatment regimen for patients with severe major depression, including those with psychotic features or catatonia, is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Catatonia: Treatment and prognosis" and "Major depressive disorder in adults: Approach to initial management", section on 'Choosing a treatment regimen for patients with major depression'.)

- **SNRIs or SSRIs as preferred antidepressants** – For the initial treatment of severe major depression, we suggest serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine or duloxetine, although selective serotonin reuptake inhibitors (SSRIs), such as escitalopram or sertraline, are a reasonable alternative. Some experts prefer SNRIs because they may be superior to SSRIs in achieving remission in those with severe major

depression (table 6) [61]. Nevertheless, many patients with severe depression respond to SSRIs, which are superior to placebo for the treatment of severe major depression, are generally well tolerated, and have a low risk of life-threatening toxicity in overdose [62]. (See 'General preference for SSRIs' above.)

Clinically important differences in efficacy or tolerability between the SNRIs are not apparent. However, we suggest carefully monitoring the use of venlafaxine in persons with hypertension since venlafaxine (especially the immediate-release formulation) can occasionally cause dose-dependent increases in diastolic blood pressure. (See 'Caution with certain comorbidities' above.)

Using an SNRI is supported by meta-analyses of randomized trials that suggest severe major depression may respond better to SNRIs than SSRIs [61,63,64]. Representative studies include:

- A meta-analysis of 31 trials compared the SNRI venlafaxine with SSRIs (primarily fluoxetine and paroxetine) and stratified participants by baseline depression severity [63]. In the 656 patients with severe depression (score ≥30 on the Hamilton Rating Scale for Depression (table 9)), remission was more likely in those randomized to venlafaxine than SSRIs (OR 1.6, 95% CI 1.1-2.2, number needed to treat = 11).

- In a meta-analysis of 15 trials, remission occurred more often in the subgroup of hospitalized patients (n = 582) who received SNRIs (duloxetine, milnacipran, and venlafaxine) than SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; 52 versus 29 percent, respectively) [64].

- **Alternative agents** – TCAs and mirtazapine are alternative options for patients with severe major depression (table 6). TCAs also have demonstrated efficacy in treating severe MDD but greater safety hazards. Tailoring antidepressants to address specific depressive symptoms or patient comorbidities or avoid certain side effects is also a reasonable alternative strategy (table 8). (See 'Tailoring antidepressant selection' above.)

  - Mirtazapine – Mirtazapine is effective for treating patients with severe major depression [65-67]. Although a meta-analysis comparing the efficacy of mirtazapine with SSRIs and SNRIs found that participants were more likely to achieve an early response (at two weeks) with mirtazapine, rates of remission were similar with all agents [65]. Side effects of sedation and weight gain also limit the use of mirtazapine in some patients.

- Tricyclic antidepressants – TCAs are efficacious for severely depressed patients, although they are frequently avoided due to their greater safety hazards (eg, cardiotoxicity and potential lethality with overdose), less-favorable side effect profiles, and lower tolerability (table 7) [18]. As an example, a meta-analysis of 1377 hospitalized patients found greater symptom improvement with TCAs (particularly amitriptyline) than SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine), although the clinical difference was small [68]. Moreover, treatment discontinuation due to adverse effects occurred more frequently with TCAs (14 versus 9 percent). By contrast, a subsequent meta-analysis of 54 trials of hospitalized patients with depression failed to show a significant difference in response rates among participants randomized to amitriptyline versus SSRIs (OR for SSRI 1.37, 0.87-1.96) [69]. Differences in patient populations and depression characteristics (eg, severity, chronicity) may account for these discrepant findings.

INITIAL ADMINISTRATION

Patient education — We counsel patients about the rationale for antidepressant treatment, how to take the medication and address side effects, and the importance of medication adherence and ongoing monitoring [70,71]. Specific guidance for patient education appears in a table (table 10).

Although the efficacy of education alone for improving depression outcomes is not supported by existing evidence, education combined with other interventions to improve depression management has been associated with improved adherence and outcomes [72]. Given that education likely has minimal harms and adherence to antidepressants is often poor, it is reasonable to provide psychoeducation to help to strengthen a therapeutic alliance and address potential adherence issues [73]. Adherence to depression management is discussed separately. (See "Depression in adults: General principles and prognosis", section on 'Adherence to treatment'.)

Initial low dose and dose titration — We suggest starting antidepressants at low doses to reduce side effects and improve adherence and then increasing the dose as tolerated to reach a therapeutic range [74]. Typical starting doses appear in a table (table 6).

Starting at one-half the normal initial dose may further reduce adverse effects and decrease early discontinuation of the medication. This approach may benefit patients who are older, are receiving polypharmacy, have a comorbid anxiety disorder, or are sensitive to side effects. For patients who start at one-half the normal initial dose, it is important to titrate up to the

minimum usual total daily dose (therapeutic dose) over one to three weeks, depending upon tolerability. (Related Pathway(s): Unipolar major depression: Initial pharmacologic therapy in adults.)

Further dose adjustment at two to four weeks — For individuals who do not respond to the minimum therapeutic dose of an antidepressant (not the starting dose) within two to four weeks, we suggest increasing the dose as tolerated toward the upper end of the usual dosing range (table 6) [36,75,76].

Dose adjustment can proceed rapidly if the patient is tolerating the medication without significant side effects. However, patients who have side effects or reluctance to increase the medication for other reasons may need more gradual dose titration. For these individuals, continuing the initial standard dose is a reasonable alternative because some of these patients will ultimately respond. We do not consider switching antidepressants until the patient has undergone an adequate treatment trial. (See 'Ensure duration of adequate trial' below.)

- Evidence that supports increasing the antidepressant dose includes a meta-analysis of 40 randomized trials that compared different doses of selective serotonin reuptake inhibitors (SSRIs) with placebo in patients with major depression (n>10,000) [77]. Improvement with SSRIs was greater at higher doses than lower doses, and the increased efficacy with higher doses outweighed the higher rate of treatment discontinuation due to side effects. The clinical benefit of higher doses was small and appeared to plateau at the upper end of the usual dose range (eg, 50 mg/day of fluoxetine). Dose increase is consistent with suggestions in multiple practice guidelines [17,18,23,71,74].

- However, continuing the same dose is also a reasonable approach because response rates to an antidepressant generally improve the longer the patient continues treatment, and some depressive episodes remit even without treatment. As an example, a meta-analysis of nine trials included participants who did not respond to an initial standard dose of an SSRI or serotonin-norepinephrine reuptake inhibitor after three to nine weeks and were then randomized either to continue the initial dose or increase it (eg, fluoxetine 20 mg/day versus 40 to 60 mg/day) [78]. Both groups experienced comparable rates of symptom improvement and discontinuation of treatment due to adverse effects. A prior meta-analysis of six trials reported similar findings [79-81]. (See 'Address factors that can affect response' below.)

Some patients benefit from doses that exceed the maximum therapeutic dose [74]. Patients receiving high doses should be regularly monitored for adverse effects and nonadherence [82].

(See 'Address side effects' below and "Depression in adults: General principles and prognosis", section on 'Adherence to treatment'.)

Additional information about starting doses, titration schedules, and target doses of antidepressants (table 6) is discussed in topics that review specific classes of antidepressants.

MONITORING INITIAL TREATMENT

Frequency of monitoring — Patients who start an antidepressant should receive follow-up within one to two weeks to evaluate for side effects, monitor for early discontinuation, and assess for early improvement. The frequency of ongoing follow-up depends on the severity of the patient's symptoms, degree of functional impairment, medical complexity, and suicidal risk factors (eg, substance abuse, prior suicide attempts, etc); however, monitoring by telephone, telehealth, or in-person visits should occur every two to four weeks during the initial phase of antidepressant management to promote adherence, timely dose adjustments, and early detection of adverse events. (See "Major depressive disorder in adults: Approach to initial management", section on 'Ongoing monitoring and follow-up'.)

Assessing treatment response — Patients should complete symptom rating scales at each follow-up to monitor their response to treatment. We use the nine-item Patient Health Questionnaire (PHQ-9) scale to monitor symptoms in patients with depression because it is a short, self-administered, widely available scale that has been extensively validated in diverse patient populations and different languages (table 4) [83-88]. Using symptom scales to inform dosing adjustments can potentially improve treatment outcomes, more quickly identify nonresponse and response, recognize remission, and help to engage patients in treatment. Details regarding the use of the PHQ-9 and other symptom scales to monitor depression are discussed separately. (See "Major depressive disorder in adults: Approach to initial management", section on 'Ongoing monitoring and follow-up' and "Using scales to monitor symptoms and treat depression (measurement based care)".)

Address side effects

- **Ask about side effects** – We ask about side effects at each visit, particularly during the initial weeks of treatment, because they are a common reason for discontinuing antidepressants and they inform dose adjustments. Patients who develop side effects should receive education that most are temporary. With selective serotonin reuptake inhibitors (SSRIs), the most common early side effects include insomnia, increased activation or anxiety, and nausea and/or diarrhea (table 7). Given the likelihood that

these will resolve after several weeks, individuals who develop but can tolerate them should continue the antidepressant if possible. Adverse effects that do not resolve with time include sexual dysfunction, corrected QT interval prolongation, hyponatremia, and blood pressure elevation. Patients whose side effects do not resolve and/or who have intolerable side effects can try a lower dose of the antidepressant or switch to an alternative antidepressant.

Over half of individuals who newly start antidepressants will have side effects; however, most of these resolve within the first two weeks. Unless clinicians ask about them specifically, side effects can go undetected and can interfere with adherence to antidepressants [89,90]. In addition, the degree to which antidepressant side effects interfere with daily functioning is associated with poorer treatment outcomes, including response and remission [91].

Symptom scales can help to identify and quantify side effects. Self-report instruments to assess side effects include the Toronto Side Effects Scale (table 11) and the Frequency, Intensity, and Burden of Side Effects Rating Scale (figure 3). Although some data indicate that side effects scales are more effective than usual practice for identifying frequent and significantly bothersome adverse effects, it is not known whether their use improves antidepressant adherence. The use of side effects scales in depression management is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Adverse side effects scale'.)

- **Watch for new-onset mania** – Because antidepressants can uncommonly precipitate mania or hypomania in individuals with undiagnosed bipolar disorder, we closely monitor for symptoms of mania or hypomania (eg, decreased need for sleep; increased irritability, aggressiveness, or agitation; euphoria; increased energy). Appearance of such symptoms should prompt an evaluation for bipolar disorder and discontinuation of the antidepressant (table 2 and table 3). The risk of "switching" from depression to mania in individuals with undiagnosed bipolar major depression who initiate treatment with antidepressants is discussed separately. (See "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants", section on 'Risk of switching to mania'.)

- **Monitor blood pressure** – We monitor blood pressure in individuals who start venlafaxine as well as patients at risk for hypertension or hypotension. This includes patients over age 65, with medical comorbidities that predispose to orthostasis (eg, Parkinson's disease), or on antihypertensive drugs or other medication that can reduce blood pressure. Because trazodone and the SSRIs can cause orthostatic hypotension, we ask about symptoms of

postural lightheadedness and check orthostatic blood pressures in those who endorse symptoms.

We check blood pressures at baseline and within two months. We typically monitor blood pressure every two to six months, especially for individuals taking higher doses of venlafaxine (≥300 mg/day). Doses of less than 300 mg per day have not been associated with significant blood pressure elevation.

- **Evaluate for uncommon side effects** – Given that SSRIs and serotonin-norepinephrine reuptake inhibitors can increase the risk of hyponatremia, individuals at high risk for hyponatremia should receive periodic monitoring of serum sodium levels [41]. These include patients who are older (>65 years), use diuretics, and/or have a history of hyponatremia. Other class-based side effects of antidepressants are discussed separately. (See "Major depressive disorder in adults: Approach to initial management", section on 'Safety of antidepressants'.)

- **When to consider stopping an antidepressant due to side effects** – Because most side effects of antidepressants are transient, we first educate about side effects and individualize medication dose titration to minimize them (see 'Initial low dose and dose titration' above). If side effects occur and are tolerable, we hold off on further dose escalation to see if they resolve or diminish. Some side effects can be adequately managed with behavioral interventions (eg, sleep hygiene for insomnia) or medications (eg, phosphodiesterase 5 inhibitors for sexual dysfunction). Side effects that persist despite these interventions and/or are severe or interfere with medication adherence warrant discontinuation of the antidepressant.

  Except for patients who develop symptoms concerning for new-onset mania, most individuals who stop an antidepressant due to side effects should start an alternative antidepressant. We try to select an antidepressant with a different side effect profile either from within the same class or from a different class, depending on the specific side effect. (See 'Avoiding specific side effects' above.)

  Symptoms that suggest new-onset mania or hypomania should prompt immediate discontinuation of the antidepressant.

Prognostic value of early improvement — Patients whose symptoms improve during the first two weeks of treatment should be encouraged to continue their antidepressant since early improvement suggests a likelihood of future response and remission.

Among individuals who ultimately respond to a given antidepressant, many experience improved symptoms within two weeks (ie, "early improvement," with improvement defined as reduction of baseline symptoms of ≥20 percent) [92-94]. As an example, a pooled analysis of four randomized trials found that, although improvement times with antidepressant treatment varied widely among participants, the mean time to improvement was approximately 13 days [95].

Early improvement at two weeks can predict future response and remission [95-100]. As an example, in a meta-analysis of 6562 individuals with MDD, early responders (those who had ≥20 percent reduction in baseline symptom score at two weeks) were more likely than those without an early response to have a sustained response at six to eight weeks (53 versus 11 percent, respectively) [101]. A subsequent study reported similar findings in a population of inpatients with major depression [102].

While early improvement seems to predict further benefit, patients without early improvement may subsequently respond or remit [103].

SUBSEQUENT MANAGEMENT

Defining response — We use symptom scales, such as the nine-item Patient Health Questionnaire (PHQ-9), to monitor changes in symptoms and determine subsequent management (table 4).

Patients with response — Response is usually defined as an improvement in symptom score of ≥50 percent that is still above the threshold for remission [9,10].

- **Treat to remission** – Clinicians should continue to monitor individuals whose symptoms respond to initial treatment to ensure that remission occurs (ie, PHQ-9 score of less than 5 that remains stable for at least one month). This may entail dose adjustment, if tolerated. Some individuals who respond to the initial treatment may ultimately require augmentation with a second medication to achieve remission. (See 'Start next-step treatment' below and "Unipolar depression in adults: Choosing treatment for resistant depression".)

- **Duration of treatment** – Once remission has been attained, individuals enter the continuation and maintenance phases of depression management (figure 1). Patients should continue antidepressant treatment for at least six months from the time they attain remission. Factors that influence the specific duration of antidepressant treatment during the continuation and maintenance phases are discussed separately. (See "Major

depressive disorder in adults: Continuation and maintenance treatment", section on 'Indications'.)

Patients with incomplete response — Individuals who do not respond or have only a partial response to treatment at four weeks should undergo assessment of potential reasons for nonresponse and have a time-limited trial of continued treatment with the same agent before proceeding to next-step treatment. Although some individuals require up to 12 weeks to respond to antidepressant treatment, we typically assess patients early on for factors that can affect response, particularly for patients with more severe depressive symptoms.

Likelihood of nonresponse — Approximately 50 to 60 percent of patients with MDD do not respond to the initial antidepressant [104-108]. As an example, in a meta-analysis of 28 randomized trials of individuals with depression in primary care (n = 5940), response rates (eg, reduction of baseline symptoms ≥50 percent) at six to eight weeks were 63 percent [109]. In a second meta-analysis, pooled response rates from two trials of antidepressant treatment were 56 percent at 12 weeks [104]. Response rates in settings that more closely resemble a typical primary care practice tend to be lower than those in clinical trials. Prognosis with initial antidepressant treatment is discussed separately. (See "Depression in adults: General principles and prognosis", section on 'Prognosis'.)

Address factors that can affect response — When patients do not respond or have only a partial response to initial antidepressant treatment at four weeks, it is important to ask about medication adherence, ensure that the patient is taking an adequate dose, and assess for factors that may complicate response to treatment.

- **Medication adherence** – It is important to assess patients' adherence to antidepressant treatment, correct patient misunderstandings about how to take the medication, troubleshoot any identified issues with adherence, and identify and treat antidepressant side effects. (See "Depression in adults: General principles and prognosis", section on 'Adherence to treatment'.)

- **Inadequate dose** – It is important to ensure that the patient is not taking a subtherapeutic antidepressant dose and, for patients taking the lower range of the usual dose, increase the dose to the upper end of that range. Therapeutic dose ranges for antidepressants appear in a table (table 6).

  Additionally, individuals with increased cytochrome P450 2D6 (CYP2D6) activity may rapidly metabolize some antidepressants and require larger doses of antidepressants. Genetic polymorphisms or concomitant administration of medications that inhibit CYP2D6 enzymes can influence antidepressant pharmacokinetics and affect the dose required to

achieve a therapeutic serum concentration [110,111]. As an example, in a study of individuals who were treated with escitalopram and underwent cytochrome P450 2C19 genotyping, serum escitalopram concentrations were more than three times greater in those classified as poor metabolizers compared with those classified as extensive metabolizers [112]. The role of genetic factors in response to antidepressants and drug metabolism more generally are discussed separately. (See "Unipolar depression: Genetics" and "Overview of pharmacogenomics".)

- **Coexisting conditions** – Because psychosocial factors and comorbid medical diagnosis may complicate response to antidepressants, they should be evaluated for and, if possible, treated. Socioeconomic factors that have been associated with poorer prognostic outcomes include social isolation, unemployment, and unstable housing conditions [113,114]. Common psychiatric comorbidities that may complicate response to treatment include substance use disorder; anxiety disorders, including panic disorder; posttraumatic stress disorder; and attention deficit hyperactivity disorder [115]. These are discussed separately. (See "Depression in adults: Clinical features and diagnosis", section on 'Comorbidities'.)

- **Incorrect diagnosis** – Individuals who do not respond to initial antidepressant treatment should also be re-evaluated to confirm a diagnosis of major depression. Some patients may have an alternative diagnosis, such as undiagnosed bipolar disorder, that requires different pharmacotherapy. (See "Approach to the adult patient with suspected depression", section on 'Mania or hypomania'.)

Ensure duration of adequate trial — After addressing factors that may contribute to an individual's lack of response, we ensure that they have had an adequate trial of therapy. The duration of an adequate trial depends in part on whether the patient has experienced a partial or no response. We suggest that clinicians engage patients in informed decision making regarding the relative merits of continuing the initial management strategy versus proceeding to next-step treatment. (See 'Start next-step treatment' below.)

- **Patients with a partial response** – We suggest that individuals who have had a partial response to initial antidepressant treatment continue a treatment trial for a total duration of 6 to 12 weeks before proceeding to next-step treatment [116-119]. We define partial response as a reduction in symptoms of >30 but <50 percent.

  The rationale for continuing treatment in those with an initial partial response derives from evidence that some individuals require 8 to 12 weeks to achieve a response or remission. As an example, the Sequenced Treatment Alternatives to Relieve Depression

(STAR*D) study, which treated a sample that was more generalizable than those typically enrolled in clinical trials, found that nearly 25 percent of participants treated with open-label citalopram required 10 or 12 weeks of treatment to achieve remission [105]. Other observational studies have shown similar results [120,121].

Response rates to antidepressants that occur after four to six weeks still exceed those achieved with placebo. As an example, a meta-analysis of five randomized trials of second generation antidepressants found that, among participants who did not respond (reduction of baseline symptoms ≥50 percent) after four weeks of treatment, 22 percent responded at eight weeks, compared with only 11 percent of those who received placebo [104]. An earlier meta-analysis of 28 trials found that the advantage of selective serotonin reuptake inhibitors (SSRIs) over placebo continued to increase for at least six weeks of treatment [122].

This approach is consistent with multiple practice guidelines [17-19,23].

- **Patients with nonresponse** – We suggest that patients with minimal to no response to initial antidepressant treatment should continue the treatment trial for a total duration of four to six weeks before proceeding to next-step treatment. We define nonresponse as a reduction in symptoms of less than 30 percent.

  The rationale for proceeding to next-step treatment in this subset of patients stems from the observation that rates of response and remission are low (ranging from 4 to 20 percent) among individuals who continue the same antidepressant after not responding in four weeks [101,106,123,124] (see 'Address side effects' above). Representative studies include:

  - A review of 15 randomized trials and observational studies found that, among participants who demonstrated minimal improvement (eg, reduction of baseline symptoms <20 percent) at four weeks, only 20 percent responded after four additional weeks of treatment with the same agent [106].

  - In a study of 566 patients with major depression who improved only minimally (<30 percent reduction of baseline symptoms) after four weeks of open-label escitalopram, those who were randomized to switch to duloxetine immediately were more likely to experience remission at week 16 than those who continued escitalopram or delayed a switch to duloxetine until eight weeks (43 versus 36 percent) [124].

Start next-step treatment — When patients have incomplete response to an initial antidepressant after addressing the above-mentioned issues (see 'Address factors that can

affect response' above) and completing an adequate trial, we suggest proceeding to next-step treatment [74,118,125]. Common approaches to next-step treatment include switching to a different antidepressant, augmenting the first antidepressant with a second intervention, or referring for psychotherapy [126]. For individuals with no or minimal response to a single-antidepressant trial, we suggest switching to another antidepressant, usually one from a different class (ie, switch from an SSRI to a serotonin-norepinephrine reuptake inhibitor). For individuals who have a partial response to the initial antidepressant trial, we discuss options with the patient. These include adding a second antidepressant from a different class, such as bupropion or mirtazapine, or switching to an antidepressant from a different class. The process of switching antidepressants is discussed separately. (See "Switching antidepressant medications in adults".)

We generally reserve augmentation with agents that are not antidepressants for those who have not responded to two trials of antidepressant therapy (ie, individuals with resistant depression). Treatment of individuals with resistant depression is discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

Among individuals who switch to a second antidepressant after nonresponse to the first agent, approximately 20 percent will have a remission with that agent. As an example, in the subset of participants in the STAR*D trial who did not respond to initial treatment with citalopram and were then randomized to a second antidepressant (bupropion, sertraline, or venlafaxine), 21 percent remitted, and an additional 9 percent responded without remission [103]. A significant proportion of participants required a long trial of treatment, with 50 percent of responses occurring after six weeks and 33 percent of responses occurring after at least nine weeks of treatment.

AVOID SUDDEN DISCONTINUATION

Because sudden discontinuation of antidepressants can cause withdrawal symptoms, patients who want or need to stop antidepressant treatment should gradually taper the medication [71]. Discontinuing antidepressants is discussed separately. (See "Discontinuing antidepressant medications in adults".)

Approximately 30 percent of individuals will have symptoms when they stop an antidepressant. The incidence of discontinuation symptoms varies with the specific antidepressant, pharmacokinetics, dose, and sensitivity of the patient to side effects. Discontinuation symptoms occur most frequently with medications that have short half-lives, such as paroxetine and venlafaxine, and less frequently with medications with longer half-lives, such as fluoxetine.

Common symptoms of discontinuation include dizziness, nausea, altered sensations (eg, paresthesias, shock-like sensations), increased agitation, insomnia, anxiety, and return of depressed mood.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Medicines for depression (The Basics)" and "Patient education: Coping with high drug prices (The Basics)" and "Patient education: Depression in adults (The Basics)")

- Beyond the Basics topics (see "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Goals and role of antidepressant therapy** – The goals of initial treatment for major depressive disorder (MDD) are to restore baseline functioning, induce symptom remission,

and prevent relapse. Antidepressants can be used as monotherapy or in combination with other interventions. The overall approach to the management of MDD is discussed elsewhere. (See "Major depressive disorder in adults: Approach to initial management".)

- **Antidepressant selection for mild to moderate depression** – For initial pharmacotherapy of mild to moderate MDD, we suggest a selective serotonin reuptake inhibitor (SSRI), typically escitalopram or sertraline, rather than other classes of antidepressants (**Grade 2C**). Although efficacy is similar within and across classes of antidepressants, SSRIs optimize efficacy, safety, and tolerability for most patients. Reasonable alternatives include serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, and serotonin modulators (table 6). Potential reasons to use alternatives to SSRIs are listed in a table (table 8). (See 'Patients with mild to moderate depression' above and 'Tailoring antidepressant selection' above.)

- **Antidepressant selection in severe depression** – For patients with severe MDD, we suggest SNRIs (such as venlafaxine or duloxetine) rather than other classes of antidepressants (**Grade 2C**). Some data suggest that SNRIs are superior to other agents for achieving remission in this group. SSRIs are reasonable alternatives because they are safe, efficacious, and generally well tolerated in these patients. Among other agents for treating severe depression, mirtazapine and tricyclic antidepressants are the best studied (table 6). Other antidepressants may be reasonable to address specific symptoms or side effects (table 8). (See 'Patients with severe major depression' above and 'General preference for SSRIs' above and 'Tailoring antidepressant selection' above.)

  Individuals with severe major depression may benefit from combination treatment with psychotherapy, require hospitalization and/or referral to a psychiatrist, or require specific therapies for symptoms of psychosis and catatonia. (See "Major depressive disorder in adults: Approach to initial management", section on 'Choosing a treatment regimen for patients with major depression' and "Major depressive disorder in adults: Approach to initial management".)

- **Initiating antidepressant therapy**

  - **Initial dosing** – Typical initial doses of antidepressants are low to reduce side effects and then increased to a therapeutic range (table 6). Individuals with polypharmacy, comorbid anxiety disorders, or sensitivity to medication side effects and those who are older may benefit from starting at one-half the usual initial dose and then increasing to the usual initial dose in the first two weeks. (See 'Initial low dose and dose titration' above.)

- **Dose titration** – After two to four weeks, individuals who do not respond to the minimum therapeutic dose should increase the dose to the higher end of the therapeutic range, if possible. Patients who experience side effects may need slower dose up-titration. (See 'Further dose adjustment at two to four weeks' above.)

- **Patient education** – We counsel patients about the rationale for antidepressants, potential side effects, the importance of monitoring, and the time course of improvement (table 10). (See 'Patient education' above.)

- **Monitoring**

  - **Frequency** – We have patients follow up at one to two weeks to assess for side effects, adherence, and early response to treatment. Subsequent follow-up should occur every two to four weeks during the initial phase of antidepressant management. (See 'Frequency of monitoring' above.)

  - **Assessments** – At each visit, we use a validated self-report scale to monitor treatment response, such as the nine-item Patient Health Questionnaire (table 4). (See 'Assessing treatment response' above.)

    Important or common side effects to assess include symptoms of mania or hypomania, increased agitation or anxiety, and gastrointestinal symptoms (table 7). Patients who develop symptoms of mania or hypomania should undergo evaluation for bipolar disorder, and the antidepressant should be stopped. Patients with other side effects that are intolerable or do not resolve can try a lower dose of the antidepressant or switch to an alternative antidepressant. (See 'Address side effects' above.)

- **Subsequent management**

  - **Patients who respond** – Patients who respond (ie, have reduction of baseline symptoms ≥50 percent) should continue antidepressant therapy until remission and then for at least six months (continuation phases). (See "Major depressive disorder in adults: Continuation and maintenance treatment".)

  - **Patients with incomplete response** – Patients with an incomplete response (either a partial response or nonresponse) should optimize their antidepressant dose and medication adherence. Clinicians should address comorbidities that impact treatment response and ensure an adequate trial of therapy (four to twelve weeks) before proceeding to next steps. Potential next steps include switching to a different

antidepressant or augmenting the first antidepressant with a second intervention. (See 'Patients with incomplete response' above.)

- **Avoiding sudden discontinuation** – Individuals who want or need to stop their antidepressant should gradually taper the medication to avoid discontinuation symptoms. (See "Discontinuing antidepressant medications in adults".)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Gregory Simon, MD, MPH, who contributed to an earlier version of this topic review.

Use of UpToDate is subject to the Terms of Use.

REFERENCES

1. Kessler RC, Ormel J, Petukhova M, et al. Development of lifetime comorbidity in the World Health Organization world mental health surveys. Arch Gen Psychiatry 2011; 68:90.
2. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003; 54:216.
3. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA 2013; 310:591.
4. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2197.
5. Thornicroft G, Chatterji S, Evans-Lacko S, et al. Undertreatment of people with major depressive disorder in 21 countries. Br J Psychiatry 2017; 210:119.
6. Solomon DA, Keller MB, Leon AC, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry 2000; 157:229.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Text Revision (DSM-5-TR), American Psychiatric Association, 2022.
8. Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, et al. Nonpharmacologic and Pharmacologic Treatments of Adults in the Acute Phase of Major Depressive Disorder: A Living Clinical Guideline From the American College of Physicians. Ann Intern Med 2023; 176:239.
9. Zhang C, Virani S, Mayes T, et al. Toward a Definition of "No Meaningful Benefit" From Antidepressant Treatment: An Equipercentile Analysis With Cross-Trial Validation Across

Multiple Rating Scales. J Clin Psychiatry 2022; 83.

10. Conway CR, Kumar A, Xiong W, et al. Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment-Resistant Major Depression. J Clin Psychiatry 2018; 79.
11. Judd LL, Schettler PJ, Rush AJ, et al. A New Empirical Definition of Major Depressive Episode Recovery and Its Positive Impact on Future Course of Illness. J Clin Psychiatry 2016; 77:1065.
12. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. Neuropsychopharmacology 2006; 31:1841.
13. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991; 48:851.
14. Dunlop BW, Holland P, Bao W, et al. Recovery and subsequent recurrence in patients with recurrent major depressive disorder. J Psychiatr Res 2012; 46:708.
15. Jarrett RB, Thase ME. Comparative efficacy and durability of continuation phase cognitive therapy for preventing recurrent depression: design of a double-blinded, fluoxetine- and pill placebo-controlled, randomized trial with 2-year follow-up. Contemp Clin Trials 2010; 31:355.
16. Zimmerman M, Walsh E, Friedman M, et al. Identifying Remission From Depression on 3 Self-Report Scales. J Clin Psychiatry 2017; 78:177.
17. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Maj or Depressive Disorder, 3rd ed, 2010. https://psychiatryonline.org/guidelines (Accessed on April 17, 2012).
18. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol 2015; 29:459.
19. Bauer M, Pfennig A, Severus E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry 2013; 14:334.
20. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2015; 49:1087.

21. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905.
22. Gartlehner G, Thaler K, Hill S, Hansen RA. How should primary care doctors select which antidepressants to administer? Curr Psychiatry Rep 2012; 14:360.
23. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry 2016; 61:540.
24. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391:1357.
25. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med 2011; 155:772.
26. Simon GE, Perlis RH. Personalized medicine for depression: can we match patients with treatments? Am J Psychiatry 2010; 167:1445.
27. Linde K, Kriston L, Rücker G, et al. Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis. Ann Fam Med 2015; 13:69.
28. Gartlehner G, Hansen RA, Morgan LC, et al. Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression: An Update of the 2007 Comparative Effectiveness Review, Agency for Healthcare Research and Quality (US), 2011.
29. Budenholzer B. Review: In major depressive disorder, antidepressant drugs improve short-term response compared with placebo. Ann Intern Med 2018; 168:JC67.
30. Wagner G, Schultes MT, Titscher V, et al. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: A systematic review and network meta-analysis. J Affect Disord 2018; 228:1.
31. Taliaz D, Spinrad A, Barzilay R, et al. Optimizing prediction of response to antidepressant medications using machine learning and integrated genetic, clinical, and demographic data. Transl Psychiatry 2021; 11:381.
32. Athreya AP, Neavin D, Carrillo-Roa T, et al. Pharmacogenomics-Driven Prediction of Antidepressant Treatment Outcomes: A Machine-Learning Approach With Multi-trial Replication. Clin Pharmacol Ther 2019; 106:855.

33. Schwartzmann B, Dhami P, Uher R, et al. Developing an Electroencephalography-Based Model for Predicting Response to Antidepressant Medication. JAMA Netw Open 2023; 6:e2336094.
34. Marcus SC, Olfson M. National trends in the treatment for depression from 1998 to 2007. Arch Gen Psychiatry 2010; 67:1265.
35. Mojtabai R, Olfson M. National patterns in antidepressant treatment by psychiatrists and general medical providers: results from the national comorbidity survey replication. J Clin Psychiatry 2008; 69:1064.
36. Spijker J, Nolen WA. An algorithm for the pharmacological treatment of depression. Acta Psychiatr Scand 2010; 121:180.
37. Treviño LA, Ruble MW, Treviño K, et al. Antidepressant Medication Prescribing Practices for Treatment of Major Depressive Disorder. Psychiatr Serv 2017; 68:199.
38. Fava GA, Gatti A, Belaise C, et al. Withdrawal Symptoms after Selective Serotonin Reuptake Inhibitor Discontinuation: A Systematic Review. Psychother Psychosom 2015; 84:72.
39. Khoo AL, Zhou HJ, Teng M, et al. Network Meta-Analysis and Cost-Effectiveness Analysis of New Generation Antidepressants. CNS Drugs 2015; 29:695.
40. Ramsberg J, Asseburg C, Henriksson M. Effectiveness and cost-effectiveness of antidepressants in primary care: a multiple treatment comparison meta-analysis and cost-effectiveness model. PLoS One 2012; 7:e42003.
41. McCarron RM, Shapiro B, Rawles J, Luo J. Depression. Ann Intern Med 2021; 174:ITC65.
42. Thaler KJ, Morgan LC, Van Noord M, et al. Comparative effectiveness of second-generation antidepressants for accompanying anxiety, insomnia, and pain in depressed patients: a systematic review. Depress Anxiety 2012; 29:495.
43. Papakostas GI, Stahl SM, Krishen A, et al. Efficacy of bupropion and the selective serotonin reuptake inhibitors in the treatment of major depressive disorder with high levels of anxiety (anxious depression): a pooled analysis of 10 studies. J Clin Psychiatry 2008; 69:1287.
44. Zhou S, Li P, Lv X, et al. Adverse effects of 21 antidepressants on sleep during acute-phase treatment in major depressive disorder: a systemic review and dose-effect network meta-analysis. Sleep 2023; 46.
45. Birkinshaw H, Friedrich CM, Cole P, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. Cochrane Database Syst Rev 2023; 5:CD014682.
46. Calvi A, Fischetti I, Verzicco I, et al. Antidepressant Drugs Effects on Blood Pressure. Front Cardiovasc Med 2021; 8:704281.

47. Behlke LM, Lenze EJ, Carney RM. The Cardiovascular Effects of Newer Antidepressants in Older Adults and Those With or At High Risk for Cardiovascular Diseases. CNS Drugs 2020; 34:1133.
48. Wu CS, Liu HY, Tsai HJ, Liu SK. Seizure Risk Associated With Antidepressant Treatment Among Patients With Depressive Disorders: A Population-Based Case-Crossover Study. J Clin Psychiatry 2017; 78:e1226.
49. Nagashima T, Hayakawa T, Akimoto H, et al. Identifying Antidepressants Less Likely to Cause Hyponatremia: Triangulation of Retrospective Cohort, Disproportionality, and Pharmacodynamic Studies. Clin Pharmacol Ther 2022; 111:1258.
50. Sinyor M, Cheung CP, Abraha HY, et al. Antidepressant-placebo differences for specific adverse events in major depressive disorder: A systematic review. J Affect Disord 2020; 267:185.
51. Blumenthal SR, Castro VM, Clements CC, et al. An electronic health records study of long-term weight gain following antidepressant use. JAMA Psychiatry 2014; 71:889.
52. Arterburn D, Sofer T, Boudreau DM, et al. Long-Term Weight Change after Initiating Second-Generation Antidepressants. J Clin Med 2016; 5.
53. Petimar J, Young JG, Yu H, et al. Medication-Induced Weight Change Across Common Antidepressant Treatments : A Target Trial Emulation Study. Ann Intern Med 2024; 177:993.
54. Gafoor R, Booth HP, Gulliford MC. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study. BMJ 2018; 361:k1951.
55. Papakostas GI. The efficacy, tolerability, and safety of contemporary antidepressants. J Clin Psychiatry 2010; 71 Suppl E1:e03.
56. Chiwanda L, Cordiner M, Thompson AT, Shajahan P. Long-term antidepressant treatment in general practice: changes in body mass index. BJPsych Bull 2016; 40:310.
57. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010; 71:1259.
58. Bala A, Nguyen HMT, Hellstrom WJG. Post-SSRI Sexual Dysfunction: A Literature Review. Sex Med Rev 2018; 6:29.
59. Ben-Sheetrit J, Aizenberg D, Csoka AB, et al. Post-SSRI Sexual Dysfunction: Clinical Characterization and Preliminary Assessment of Contributory Factors and Dose-Response Relationship. J Clin Psychopharmacol 2015; 35:273.
60. Chekroud AM, Gueorguieva R, Krumholz HM, et al. Reevaluating the Efficacy and Predictability of Antidepressant Treatments: A Symptom Clustering Approach. JAMA Psychiatry 2017; 74:370.

61. Bradley AJ, Lenox-Smith AJ. Does adding noradrenaline reuptake inhibition to selective serotonin reuptake inhibition improve efficacy in patients with depression? A systematic review of meta-analyses and large randomised pragmatic trials. J Psychopharmacol 2013; 27:740.
62. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. J Psychiatr Res 2007; 41:189.
63. Schmitt AB, Bauer M, Volz HP, et al. Differential effects of venlafaxine in the treatment of major depressive disorder according to baseline severity. Eur Arch Psychiatry Clin Neurosci 2009; 259:329.
64. Machado M, Iskedjian M, Ruiz I, Einarson TR. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. Curr Med Res Opin 2006; 22:1825.
65. Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressive agents for depression. Cochrane Database Syst Rev 2011; :CD006528.
66. van Moffaert M, de Wilde J, Vereecken A, et al. Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. Int Clin Psychopharmacol 1995; 10:3.
67. Guelfi JD, Ansseau M, Timmerman L, et al. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol 2001; 21:425.
68. Anderson IM. SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety 1998; 7 Suppl 1:11.
69. Guaiana G, Barbui C, Hotopf M. Amitriptyline for depression. Cochrane Database Syst Rev 2007; :CD004186.
70. Dell'Osso B, Albert U, Carrà G, et al. How to improve adherence to antidepressant treatments in patients with major depression: a psychoeducational consensus checklist. Ann Gen Psychiatry 2020; 19:61.
71. Depression in Adults: Treatment and Management, National Institute for Health and Care E xcellence, 2022.
72. Chong WW, Aslani P, Chen TF. Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. Int J Clin Pract 2011; 65:954.
73. Mitchell AJ. Depressed patients and treatment adherence. Lancet 2006; 367:2041.
74. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2021;

55:7.

75. Ruhé HG, Huyser J, Swinkels JA, Schene AH. Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder: systematic review. Br J Psychiatry 2006; 189:309.
76. Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. CNS Drugs 2010; 24:131.
77. Jakubovski E, Varigonda AL, Freemantle N, et al. Systematic Review and Meta-Analysis: Dose-Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disorder. Am J Psychiatry 2016; 173:174.
78. Rink L, Braun C, Bschor T, et al. Dose Increase Versus Unchanged Continuation of Antidepressants After Initial Antidepressant Treatment Failure in Patients With Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized, Double-Blind Trials. J Clin Psychiatry 2018; 79.
79. Dold M, Bartova L, Rupprecht R, Kasper S. Dose Escalation of Antidepressants in Unipolar Depression: A Meta-Analysis of Double-Blind, Randomized Controlled Trials. Psychother Psychosom 2017; 86:283.
80. Johnson CF, Maxwell M, Williams B, et al. Dose-response effects of selective serotonin reuptake inhibitor monotherapy for the treatment of depression: systematic review of reviews and meta-narrative synthesis. BMJ Med 2022; 1:e000017.
81. Braun C, Adams A, Rink L, et al. In search of a dose-response relationship in SSRIs-a systematic review, meta-analysis, and network meta-analysis. Acta Psychiatr Scand 2020; 142:430.
82. Malhi GS, Hitching R, Berk M, et al. Pharmacological management of unipolar depression. Acta Psychiatr Scand Suppl 2013; :6.
83. Duffy FF, Chung H, Trivedi M, et al. Systematic use of patient-rated depression severity monitoring: is it helpful and feasible in clinical psychiatry? Psychiatr Serv 2008; 59:1148.
84. Solberg LI, Glasgow RE, Unützer J, et al. Partnership research: a practical trial design for evaluation of a natural experiment to improve depression care. Med Care 2010; 48:576.
85. Kendrick T, Dowrick C, McBride A, et al. Management of depression in UK general practice in relation to scores on depression severity questionnaires: analysis of medical record data. BMJ 2009; 338:b750.
86. Zandi PP, Wang YH, Patel PD, et al. Development of the National Network of Depression Centers Mood Outcomes Program: A Multisite Platform for Measurement-Based Care. Psychiatr Serv 2020; 71:456.

87. Gelenberg AJ. Using assessment tools to screen for, diagnose, and treat major depressive disorder in clinical practice. J Clin Psychiatry 2010; 71 Suppl E1:e01.
88. Spitzer RL, Kroenke K, Williams JB. Patient Health Questionnaire (PHQ). In: Handbook of Psy chiatric Measures, 2nd ed, Rush AJ Jr, First MB, Blacker D (Eds), American Psychiatric Associ ation Publishing, 2008. p.58.
89. Goethe JW, Woolley SB, Cardoni AA, et al. Selective serotonin reuptake inhibitor discontinuation: side effects and other factors that influence medication adherence. J Clin Psychopharmacol 2007; 27:451.
90. Bull SA, Hu XH, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. JAMA 2002; 288:1403.
91. Braund TA, Tillman G, Palmer DM, et al. Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: an iSPOT-D report. Transl Psychiatry 2021; 11:417.
92. Uher R, Mors O, Rietschel M, et al. Early and delayed onset of response to antidepressants in individual trajectories of change during treatment of major depression: a secondary analysis of data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. J Clin Psychiatry 2011; 72:1478.
93. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry 2005; 66:148.
94. Papakostas GI, Perlis RH, Scalia MJ, et al. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. J Clin Psychopharmacol 2006; 26:56.
95. Stassen HH, Angst J, Hell D, et al. Is there a common resilience mechanism underlying antidepressant drug response? Evidence from 2848 patients. J Clin Psychiatry 2007; 68:1195.
96. Katz MM, Meyers AL, Prakash A, et al. Early symptom change prediction of remission in depression treatment. Psychopharmacol Bull 2009; 42:94.
97. Ciudad A, Álvarez E, Roca M, et al. Early response and remission as predictors of a good outcome of a major depressive episode at 12-month follow-up: a prospective, longitudinal, observational study. J Clin Psychiatry 2012; 73:185.
98. Jakubovski E, Bloch MH. Prognostic subgroups for citalopram response in the STAR*D trial. J Clin Psychiatry 2014; 75:738.
99. Funaki K, Nakajima S, Suzuki T, et al. Early Improvements in Individual Symptoms to Predict Later Remission in Major Depressive Disorder Treated With Mirtazapine. J Clin Pharmacol

2016; 56:1111.

100. Kato M, Takekita Y, Koshikawa Y, et al. Non response at week 4 as clinically useful indicator for antidepressant combination in major depressive disorder. A sequential RCT. J Psychiatr Res 2017; 89:97.
101. Szegedi A, Jansen WT, van Willigenburg AP, et al. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. J Clin Psychiatry 2009; 70:344.
102. Henkel V, Seemüller F, Obermeier M, et al. Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. J Affect Disord 2009; 115:439.
103. Rush AJ, South C, Jha MK, et al. What to Expect When Switching to a Second Antidepressant Medication Following an Ineffective Initial SSRI: A Report From the Randomized Clinical STAR*D Study. J Clin Psychiatry 2020; 81.
104. Henssler J, Kurschus M, Franklin J, et al. Trajectories of Acute Antidepressant Efficacy: How Long to Wait for Response? A Systematic Review and Meta-Analysis of Long-Term, Placebo-Controlled Acute Treatment Trials. J Clin Psychiatry 2018; 79.
105. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28.
106. Kudlow PA, McIntyre RS, Lam RW. Early switching strategies in antidepressant non-responders: current evidence and future research directions. CNS Drugs 2014; 28:601.
107. Gaynes BN, Rush AJ, Trivedi MH, et al. Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. J Gen Intern Med 2008; 23:551.
108. Gaynes BN, Lux LJ, Lloyd SW, et al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults, Agency for Healthcare Research and Quality (US), 2011.
109. Mulrow CD, Williams JW Jr, Chiquette E, et al. Efficacy of newer medications for treating depression in primary care patients. Am J Med 2000; 108:54.
110. Drozda K, Müller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. Pharmacotherapy 2014; 34:166.
111. D'Empaire I, Guico-Pabia CJ, Preskorn SH. Antidepressant treatment and altered CYP2D6 activity: are pharmacokinetic variations clinically relevant? J Psychiatr Pract 2011; 17:330.

112. Jukić MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. Am J Psychiatry 2018; 175:463.

113. Buckman JEJ, Saunders R, Stott J, et al. Socioeconomic Indicators of Treatment Prognosis for Adults With Depression: A Systematic Review and Individual Patient Data Meta-analysis. JAMA Psychiatry 2022; 79:406.

114. Buckman JEJ, Saunders R, Arundell LL, et al. Life events and treatment prognosis for depression: A systematic review and individual patient data meta-analysis. J Affect Disord 2022; 299:298.

115. Buckman JEJ, Saunders R, Cohen ZD, et al. The contribution of depressive 'disorder characteristics' to determinations of prognosis for adults with depression: an individual patient data meta-analysis. Psychol Med 2021; 51:1068.

116. Rush AJ. STAR*D: what have we learned? Am J Psychiatry 2007; 164:201.

117. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. J Clin Psychiatry 2009; 70 Suppl 6:16.

118. Bobo WV, Shelton RC. Treatment of depression. In: The American Psychiatric Association Publishing Textbook of Psychopharmacology, 5th ed, Schatzberg AF, Nemeroff CB (Eds), American Psychiatric Association Publishing, 2017. p.1151.

119. Parikh SV, Riba MB, Greden JF. Depressive disorders. In: The American Psychiatric Association Publishing Textbook of Psychiatry, 7th ed, Roberts LW (Ed), American Psychiatric Association Publishing, 2019. p.307.

120. Quitkin FM, Petkova E, McGrath PJ, et al. When should a trial of fluoxetine for major depression be declared failed? Am J Psychiatry 2003; 160:734.

121. Posternak MA, Baer L, Nierenberg AA, Fava M. Response rates to fluoxetine in subjects who initially show no improvement. J Clin Psychiatry 2011; 72:949.

122. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. Arch Gen Psychiatry 2006; 63:1217.

123. Tadić A, Helmreich I, Mergl R, et al. Early improvement is a predictor of treatment outcome in patients with mild major, minor or subsyndromal depression. J Affect Disord 2010; 120:86.

124. Romera I, Pérez V, Menchón JM, et al. Early switch strategy in patients with major depressive disorder: a double-blind, randomized study. J Clin Psychopharmacol 2012; 32:479.

125. McIntyre RS. When should you move beyond first-line therapy for depression? J Clin Psychiatry 2010; 71 Suppl 1:16.

126. The American Psychiatric Association Practice Guidelines for the Psychiatric Evaluation of Adults, Third Edition. American Psychiatric Association, 2016. https://psychiatryonline.org/guidelines (Accessed on August 12, 2015).

Topic 118269 Version 3.0

GRAPHICS

DSM-5-TR diagnostic criteria for a major depressive episode

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) 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 (eg, feels sad, empty, hopeless) or observations made by others (eg, 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 (eg, a change of more than 5% of body weigh 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 their 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 direct physiological effects of a substance or to another medical condition.
NOTE: Criteria A through C represent a major depressive episode.
NOTE: Responses to a significant loss (eg, 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 a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode 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 or 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 physiological effects of another medical condition.
Specify:
With anxious distress
With mixed features
With melancholic features
With atypical features
With psychotic features
With catatonia
With peripartum onset
With seasonal pattern

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright © 2013). American Psychiatric Association. All Rights Reserved. Note: These diagnostic criteria remain unchanged in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, American Psychiatric Association 2022.

Graphic 89994 Version 16.0

DSM-5-TR diagnostic criteria for manic episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least one week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (eg, feels rested after only three hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is 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.

D. The episode is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, other treatment) or to another medical condition.

NOTE: A full manic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of tha treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

NOTE: Criteria A through D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright © 2013). American Psychiatric Association. All Rights Reserved. Note: These diagnostic criteria remain unchanged in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, American Psychiatric Association 2022.

Graphic 91106 Version 8.0

DSM-5-TR diagnostic criteria for hypomanic episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least four consecutive days and present most o the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (eg, feels rested after only three hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
7. Excessive involvement in activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning o to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (eg, a drug of abuse, a medication, or other treatment).

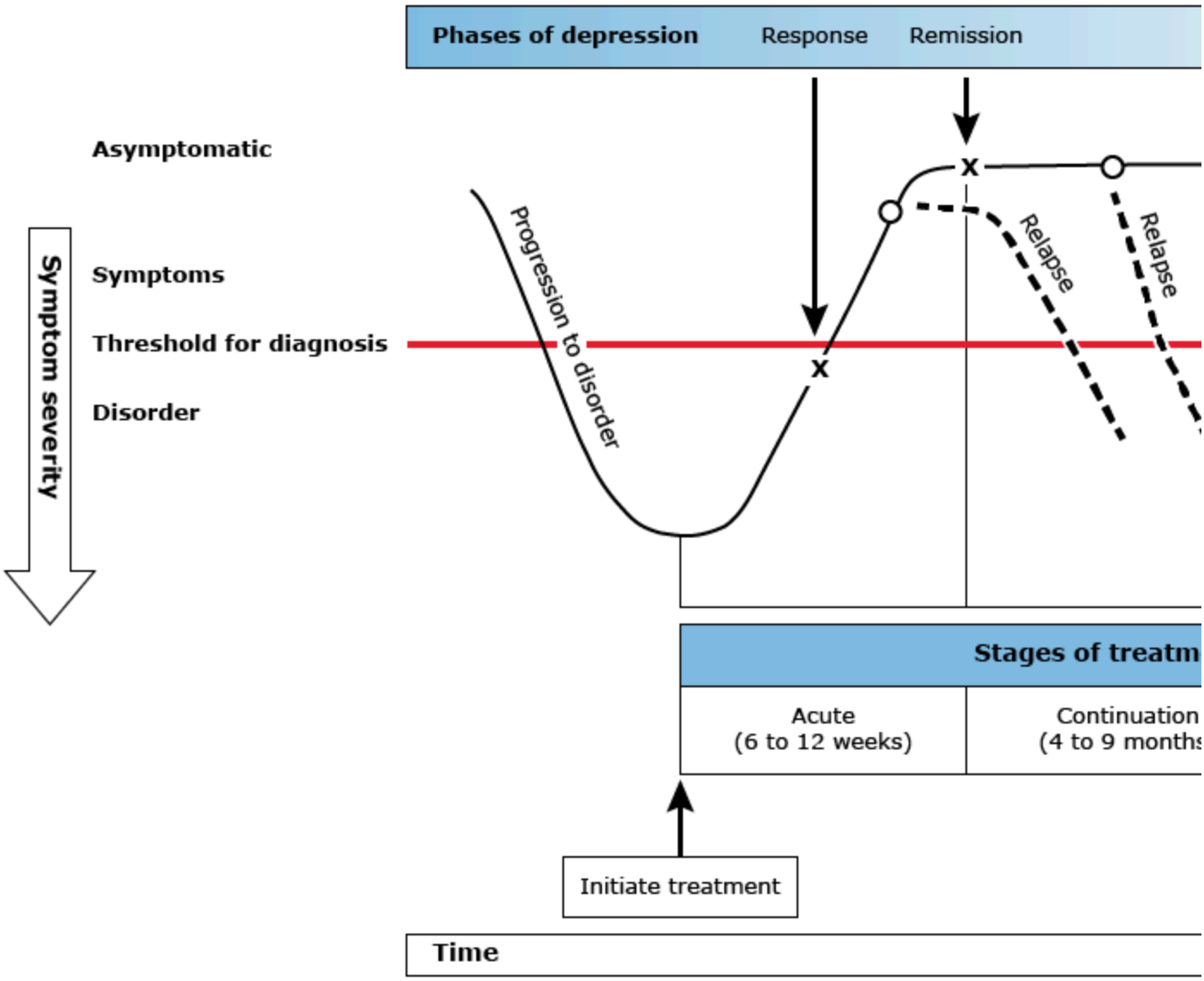
NOTE: A full hypomanic episode that emerges during antidepressant treatment (eg, medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of tha treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for a diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

NOTE: Criteria A through F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright © 2013). American Psychiatric Association. All Rights Reserved. Note: These diagnostic criteria remain unchanged in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision, American Psychiatric Association 2022.

Graphic 91107 Version 7.0

Trajectory of an episode of major depression



Trajectory and treatment stages of an episode of major depression. Varying definitions exist for the duration of each phase of depression (eg, remission, recovery) and stage of treatment (eg, acute, continuation, maintenance). Response is a clinically meaningful reduction of depressive symptoms, often defined as an improvement in symptom score of ≥50% that is still above the threshold for remission. Remission is the reduction of symptoms below the threshold for a diagnosis of major depression that is maintained for at least 2 months. Recovery occurs with the stable maintenance of no to minimal symptoms for a longer period of time. Relapse is the return of depressive symptoms prior to recovery. Recurrence is the onset of a new episode of major depression after recovery has occurred.

From: Kupfer DJ, Long-term treatment of depression, The Journal of Clinical Psychiatry. Volume 52, Pages 28-34, 1991. Copyright 1991, Physicians Postgraduate Press. Reprinted by permission.

Graphic 144349 Version 1.0

PHQ-9 depression questionnaire

Name:	**Date:**			
Over the last 2 weeks, how often have you been bothered by any of the following problems?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself, that you are a failure, or that you have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
Moving or speaking so slowly that other people could have noticed; or the opposite, being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Total ___ =	___	**+** ___	**+** ___	**+** ___
PHQ-9 score ≥10: Likely major depression				
Depression score ranges:				
5 to 9: mild				
10 to 14: moderate				
15 to 19: moderately severe				
≥20: severe				
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all ___	Somewhat difficult ___	Very difficult ___	Extremel difficult ___

PHQ: Patient Health Questionnaire.

Developed by Drs. Robert L Spitzer, Janet BW Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer, Inc. No permission required to reproduce, translate, display or distribute.

Graphic 59307 Version 13.0

Montgomery-Asberg Depression Rating Scale, page 1

OVERALL SEVERITY - The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only on rare occasions when a depressed patient is encountered who cannot be rated on the items on the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. The scale may be used for any time interval between ratings, be it weekly or otherwise but this must be recorded. Specify **one** of the reasons listed below by putting appropriate number in adjacent box.

---

1. APPARENT SADNESS - Representing despondency, gloom, and despair (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

☐ 0 - No sadness
1
2 - Looks dispirited but does brighten up without difficulty
3
4 - Appears sad and unhappy most of the time
5
6 - Looks miserable all the time. Extremely despondent.

---

2. REPORTED SADNESS - Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency, or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

☐ 0 - Occasional sadness in keeping with the circumstances
1
2 - Sad or low but brightens up without difficulty
3
4 - Pervasive feelings of sadness or gloominess. Mood still influenced by external circumstances.
5
6 - Continuous or unvarying sadness, misery, or despondency

---

3. INNER TENSION - Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration, and the extent of reassurance called for.

☐ 0 - Placid. Only fleeting inner tension.
1
2 - Occasional feelings of edginess and ill-defined discomfort
3
4 - Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty
5
6 - Unrelenting dread or anguish. Overwhelming panic.

---

continued on page 2

Montgomery, SA. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382.

Montgomery-Asberg Depression Rating Scale, page 2

4. REDUCED SLEEP - Representing the experience of reduced duration or depth of sleep compared to the patient's own normal pattern when well.

☐ 0- Sleeps as usual
1
2 - Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep
3
4 - Sleep reduced or broken by at least 2 hours
5
6 - Less than 2 or 3 hours sleep

---

5. REDUCED APPETITE - Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

☐ 0- Normal or increased appetite
1
2 - Slightly reduced appetite
3
4 - No appetite. Food is tasteless.
5
6 - Needs persuasion to eat at all

---

6. CONCENTRATION DIFFICULTIES - Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

☐ 0 - No difficulties in concentrating
1
2 - Occasional difficulties in collecting one's thoughts
3
4 - Difficulties in concentrating and sustaining thought which reduces ability to read or hold conversation
5
6 - Unable to read or converse without great difficulty

---

7. LASSITUDE - Representing a difficulty getting started or slowness initiating and performing everyday activities.

☐ 0 - Hardly any difficulty in getting started. No sluggishness.
1
2 - Difficulties in starting activities
3
4 - Difficulties in starting simple routine activities which are carried out with effort
5
6 - Complete lassitude. Unable to do anything without help.

---

continued on page 3

Montgomery, SA. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382.

Graphic 67951 Version 2.0

Montgomery-Asberg Depression Rating Scale, page 3

8. INABILITY TO FEEL - Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

☐ 0 - Normal interest in surroundings and in other people
1
2 - Reduced ability to enjoy usual interests
3
4 - Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5
6 - The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure and a complete or even painful failure to feel for close relatives and friends

---

9. PESSIMISTIC THOUGHTS - Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.

☐ 0 - No pessimistic thoughts
1
2 - Fluctuating ideas of failure, self-reproach, or self-depreciation
3
4 - Persistent self-accusations or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 - Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

---

10. SUICIDAL THOUGHTS - Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicide attempts should not in themselves influence the rating.

☐ 0 - Enjoys life or takes it as it comes
1
2 - Weary of life. Only fleeting suicidal thoughts.
3
4 - Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 - Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Montgomery, SA. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382.

Graphic 81162 Version 3.0

Severity of depression

The severity of depression is determined by a combination of symptom number, frequency, severity, and duration and the degree of functional impairment.

Severity

Mild

Individuals with mild major depression have ≥5 symptoms of depression **and** a PHQ-9 score of 5 to 9. They generally do not have:

- Marked distress or significant functional impairment
- Frequent suicidal or homicidal ideation or plans
- Psychotic features (eg, delusions or hallucinations)
- Catatonic features (eg, immobility, mutism, excessive purposeless motor activity)
- Significant aggressiveness

Moderate

Individuals with moderate major depression have ≥5 symptoms of depression **and** a PHQ-9 score of 10 to 19. They may have suicidal or homicidal ideation and plans. They generally do not have:

- Psychotic features (eg, delusions or hallucinations)
- Catatonic features (eg, immobility, mutism, excessive purposeless motor activity)
- Marked distress or functional impairment

Severe

Individuals with severe major depression have ≥7 symptoms of depression **or** a PHQ-9 score of ≥20 **or** any of the following:

- Psychotic features (eg, delusions or hallucinations)
- Catatonic features (eg, immobility, mutism, excessive purposeless motor activity)
- Marked distress or functional impairment
- Very likely to have suicidal or homicidal ideation and behavior (ie, a specific plan and intent to act upon it)

Symptoms of major depression

An episode of major depression consists of a period of at least 2 consecutive weeks with 5 or more of the following symptoms. Symptoms must be present nearly every day, and at least 1 of the symptoms must be depressed mood or anhedonia:

- Depressed mood
- Anhedonia (decreased interest or pleasure in activities previously considered enjoyable)
- Unintended change in appetite or weight
- Insomnia or hypersomnia
- Psychomotor agitation or significant slowing
- Decreased energy or fatigue

- Feelings of worthlessness or excessive guilt
- Poor concentration or new indecisiveness
- Recurrent thoughts about death or suicide

PHQ-9: 9-item Patient Health Questionnaire.

References:

1. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Text Revision (DSM-5-TR), American Psychiatric Association 2022.*
2. *World Health Organization. Clinical Descriptions and Diagnostic Requirements for ICD-11 Mental, Behavioural and Neurodevelopmental Disorders, World Health Organization, 2024.*

Graphic 144739 Version 2.0

Depression in adults: Antidepressant doses*

Drug	Usual total starting dose per day (mg)¶	Usual total maintenance dose per day (mg)¶	Extreme daily dose range (mg)¶
Selective serotonin reuptake inhibitors			
Citalopram	20	20 to 40Δ	10 to 40Δ
Escitalopram	10	10 to 20	5 to 30
Fluoxetine	20	20 to 60	10 to 80
Fluvoxamine	50	100 to 200	25 to 300
Fluvoxamine CR	100	100 to 200	100 to 300
Paroxetine	20	20 to 40	10 to 50
Paroxetine CR	25	25 to 50	12.5 to 62.5
Sertraline	50	50 to 200	25 to 300
Serotonin-norepinephrine reuptake inhibitors			
Desvenlafaxine	25 to 50	50 to 100	50 to 400◇
Duloxetine	30 to 60	60	30 to 120§
Levomilnacipran	20	40 to 80	20 to 120
Milnacipran	12.5	100 to 200	50 to 300
Venlafaxine	37.5 to 75	75 to 375	75 to 375
Venlafaxine XR	37.5 to 75	75 to 225	75 to 375
Atypical agents			
Agomelatine¥ (not available in United States)	25	25 to 50	25 to 50
Bupropion	200	300 (maximum single dose 150 mg)	100 to 450
Bupropion SR 12 hour	150	300 (maximum single dose 200 mg)	150 to 400
Bupropion XL 24 hour	150	300	150 to 450 (United States) 150 to 300 (Europe)
Bupropion hydrobromide 24	174	348	174 to 522

hour			
Mirtazapine	15	15 to 45	7.5 to 60
Serotonin modulators			
Nefazodone‡	200	300 to 600	50 to 600
Trazodone	100	200 to 400	100 to 600
Vilazodone	10	40	10 to 40
Vortioxetine	10	20	5 to 20
Tricyclics and tetracyclics†			
Amitriptyline	25	150 to 300	10 to 300
Amoxapine	25	200 to 300	25 to 400
Clomipramine	25	100 to 250	25 to 300
Desipramine	25	150 to 300	25 to 300
Doxepin	25	100 to 300	10 to 300
Imipramine	25	150 to 300	10 to 300
Maprotiline	25	100 to 225	25 to 225
Nortriptyline	25	50 to 150	10 to 200
Protriptyline	10	15 to 60	5 to 60
Trimipramine	25	150 to 300	25 to 300
Monoamine oxidase inhibitors†			
Isocarboxazid	10	10 to 40	10 to 60
Phenelzine	15	15 to 90	7.5 to 90
Selegiline transdermal	6 mg/24-hour patch	6 to 12 mg/24-hour patch	6 to 12 mg/24-hour patch
Tranylcypromine	10	30 to 60	10 to 60

CR: controlled release; SR: sustained release; XL: extended release; XR: extended release.

* Total daily oral doses shown in table may need to be given as 2 or 3 equally divided doses per day, depending on specific antidepressant and other factors. For additional detail, refer to individual Lexidrug monographs included with UpToDate.

¶ Lower doses may be useful for initiating or maintaining patients who are older or medically compromised (eg, kidney or liver disease) or drug-sensitive patients, as well as patients with a low body mass index. High doses may be used for medications that are well tolerated but ineffective at lower doses. In patients with panic disorder, UpToDate contributors initiate treatment at one-half or less of the usual starting dose shown and titrate more gradually; refer to UpToDate topics on the management of panic disorder.

Δ Maximum recommended dose of citalopram is 20 mg for patients >60 years of age, with significant hepatic insufficiency, or taking interacting medications that can increase citalopram levels. For more information, refer to the UpToDate topic on unipolar depression in adults and selective serotonin reuptake inhibitors.

◇ Although desvenlafaxine doses up to 400 mg per day have been studied, there is no evidence that doses >50 mg per day provide any additional benefit.

§ Although duloxetine doses >60 mg/day did not confer additional benefit in clinical trials, individual patients may benefit from dose escalation up to a maximum of 120 mg/day.

¥ Agomelatine may be hepatotoxic and is contraindicated with any degree of liver impairment. Transaminase monitoring is required.

‡ Caution: Nefazodone can cause liver failure and has been withdrawn from the market in several countries. Refer to UpToDate topic on serotonin modulators pharmacology, administration, and side effects for additional information.

† Conservative starting doses shown in table are lower than starting doses shown in some other references. For additional information, refer to UpToDate topics on the treatment of depression with antidepressants as well as cyclic antidepressants and monoamine oxidase inhibitors for treatment of adults with depression.

Data from:

1. *The American Psychiatric Association Publishing Textbook of Psychopharmacology, 5th edition, Schatzberg AF, Nemeroff CB (Eds), American Psychiatric Association Publishing 2017.*
2. *Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry 2016; 61:540.*
3. *Gartlehner G, Thaler K, Hill S, Hansen RA. How should primary care doctors select which antidepressants to administer? Curr Psychiatry Rep 2012; 14:360.*
4. *UpToDate Lexidrug. More information available at https://online.lexi.com/.*

Graphic 53818 Version 44.0

Side effects of antidepressant medications[1-7]

Drug	Anticholinergic	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	QT prolonga
Selective serotonin reuptake inhibitors[¶]					
Citalopram	0	0	1+	1+	2 to 3+[Δ]
Escitalopram	0	0	1+	1+	2+
Fluoxetine	0	0	2+	1+	1+
Fluvoxamine	0	1+	1+	1+	1+
Paroxetine	1+	1+	1+	2+	1+
Sertraline	0	0	2+	1+	1+
Atypical agents					
Agomelatine[§] (not available in United States)	0	1+	1+	0	0
Bupropion	0	0	2+ (immediate release) 1+ (sustained release)	0	0 to 1+[¥]
Mirtazapine	1+	4+	0	0	1+
Serotonin-norepinephrine reuptake inhibitors[¶‡]					
Desvenlafaxine[†]	0	0	1+	0	0
Duloxetine	0	0	1+	0	0
Levomilnacipran[†]	0[**]	0	0 to 1+	0 to 1+	0
Milnacipran[†]	0	1+	0	0	0
Venlafaxine[†]	0	1+	1+	0	0 to 1+[¥]
Serotonin modulators					
Trazodone	0	4+	0	1+ (hypnotic dose) 3+ (antidepressant dose)	1 to 2+

Vilazodone	0	0	2+	0	0
Vortioxetine	0	0	0	0	0
Tricyclic and tetracyclic antidepressants					
Amitriptyline	4+	4+	0	3+	1 to 2+
Amoxapine	2+	2+	2+	2+	ND§§
Clomipramine	4+	4+	1+	2+	3+
Desipramine	1+	2+	1+	2+	1 to 2+
Doxepin	3+	3+	0	2+	3+
Imipramine	3+	3+	1+	4+	3+
Maprotiline	2+	3+	0	2+	1+
Nortriptyline	2+	2+	0	1+	1 to 2+
Protriptyline	2+	1+	1+	2+	ND§§
Trimipramine	4+	4+	1+	3+	ND§§
Monoamine oxidase inhibitors					
Isocarboxazid	1+	1+	2+	2+	0
Phenelzine	1+	2+	1+	3+	0
Selegiline	1+	0	1+	1+	0
Tranylcypromine	1+	1+	2+	2+	0

Scale: 0 = none; 1+ = slight; 2+ = low; 3+ = moderate; 4+ = high; ND = inadequate data.

QTc: corrected QT interval; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

* Relative mean QTc prolongation at therapeutic doses; arrhythmogenic potential can be significantly increased in overdose (eg, for cyclic antidepressants, bupropion, citalopram, duloxetine, venlafaxine, and some others). QTc prolongation classifications are based upon US Food and Drug Administration guidance.[6] The use of other classification criteria may lead to some agents being classified differently by other sources. Refer to UpToDate topics on acquired long QT syndrome and acute antidepressant poisonings.

¶ All SSRIs and SNRIs can cause transient nausea and gastrointestinal discomfort when starting therapy or increasing dose.

Δ Based upon reports of dose-related QTc prolongation and arrhythmia, the maximum recommended dose of citalopram is 40 mg/day in most patients; for patients at increased risk of elevated serum concentrations (eg, age >60 years, significant hepatic impairment, receiving interacting medications), the maximum daily dose is 20 mg.

◇ Sertraline is associated with higher rates of diarrhea.

§ Agomelatine may be hepatotoxic and is contraindicated in any degree of liver impairment. Transaminase monitoring is required.

¥ Evidence of an association with QTc prolongation and arrhythmias is limited to overdose; available data on QTc effects of bupropion and venlafaxine at therapeutic doses are reassuring.

‡ SNRIs do not have significant anticholinergic effects. However, SNRIs can produce anticholinergic-like effects (which appear to be mediated by noradrenergic stimulation) such as dry mouth and constipation, and they should be used with caution in narrow angle glaucoma. Levomilnacipran is associated with urinary hesitancy.

† May cause persistent dose-related increases in blood pressure (primarily diastolic) and heart rate. Monitor blood pressure regularly.

** Levomilnacipran can cause dose-dependent urinary hesitancy.

¶¶ Trazodone is associated rarely with priapism, which is considered a medical emergency. Refer to UpToDate topic on serotonin modulators.

ΔΔ Gastrointestinal effects include nausea, vomiting, and diarrhea.

◇◇ Gastrointestinal forms of anticholinergic side effects include dry mouth, constipation, epigastric distress, and decreased esophagogastric tone. Refer to "Anticholinergic" data column for frequency rankings.

§§ May prolong the QT interval, but data are insufficient to identify level of risk with confidence; refer to UpToDate content on cyclic antidepressant pharmacology, administration, and side effects.

References:

1. *Wenzel-Seifert K, Wittmann M, Haen E. QTc prolongation by psychotropic drugs and the risk of torsade de pointes. Dtsch Arztebl Int 2011; 108:687.*
2. *Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second generation antidepressants in patients with major depressive disorder: Results from a systematic review with network meta-analysis. Drug Saf 2014; 37:19.*
3. *Howland RH. A benefit-risk assessment of agomelatine in the treatment of major depression. Drug Saf 2011; 34:709.*
4. *UpToDate Lexidrug. More information available at https://online.lexi.com/.*
5. *Baldwin DS, Chrones L, Florea I, et al. The safety and tolerability of vortioxetine: Analysis of data from randomized placebo-controlled trials and open-label extension studies. J Psychopharmacol 2016; 30:242.*
6. *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythic Potential for Non-Antiarrhythmic Drugs – Questions and Answers; Guidance for Industry US Food and Drug Administration, June 2017. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073161.pdf as updated August 8, 2023 (https://www.fda.gov/media/170814/download).*
7. *The American Psychiatric Association Publishing Textbook of Psychopharmacology, 5th ed, Schatzberg AF, Nemeroff CB (Eds), American Psychiatric Association Publishing 2017.*

Graphic 62488 Version 37.0

Potential reasons to select a non-SSRI antidepressant

Clinical characteristic	Potential antidepressant choice
Severe insomnia or other need for a sedating agent	Mirtazapine
Severe hypersomnia/lack of energy or other need for less sedating agent	Bupropion*¶ Reboxetine Vilazodone
Depression-related weight loss or other need for agent that can cause weight gain	Mirtazapine$^{\Delta}$
Desire for agent that is weight neutral or causes weight loss	Bupropion*¶
Desire for agent that concurrently aids in smoking cessation	Bupropion¶
Desire to treat concomitant chronic neuropathic pain	SNRI (eg, duloxetine, milnacipran) Tricyclic antidepressants$^{\diamond}$
Prior remission with agent from a different class	Previously used antidepressant
Prior or expected inability to tolerate SSRI-related sexual dysfunction	Bupropion¶ Mirtazapine Vortioxetine Vilazodone
Severe depression	SNRI (or SSRI)§ Tricyclic antidepressants or mirtazapine

For initial treatment of most individuals with mild to moderate depression, we suggest an SSRI, typically escitalopram or sertraline. SSRIs optimize efficacy and safety for most patients. However, efficacy for mild to moderate depression is similar within and across classes of antidepressants, and other antidepressants may be an attractive choice in certain circumstances. Common reasons for choosing a non-SSRI medication include undesirable medication side effects (eg, risk of erectile dysfunction with SSRIs), patient comorbidities that non-SSRIs can address (eg, neuropathic pain), patient symptoms that a specific antidepressant might treat (eg, using mirtazapine in a patient with weight loss), and history of prior antidepressant use.

SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

* Some SSRIs can be used in this clinical situation; fluoxetine is the least sedating.

¶ Bupropion is contraindicated in individuals with seizure disorder or increased risk of seizure, including anorexia nervosa and bulimia.

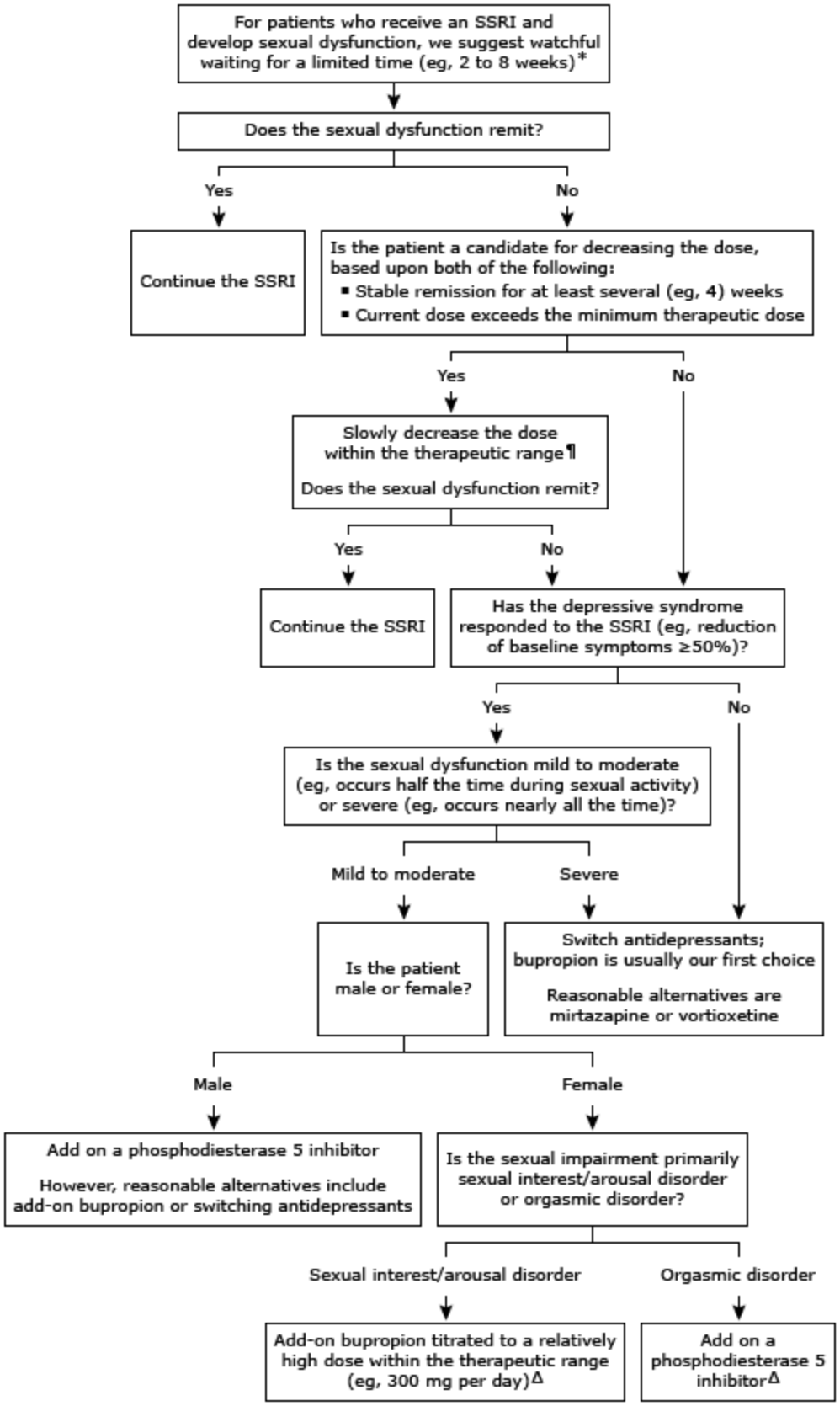
Δ Paroxetine is an SSRI that can be used in this clinical situation.

◇ Tricyclic antidepressants are effective for chronic neuropathic pain, but adverse effects and safety concerns limit their use in initial management.

§ Both SNRIs and SSRIs are reasonable first-line options for treating severe major depression.

Graphic 144370 Version 1.0

Overview of managing sexual dysfunction caused by selective serotonin reuptake inhibitors



SSRIs are first-line antidepressants for treating depressive disorders, which are widely prevalent; sexual dysfunction is one of the most common adverse effects of SSRIs. This algorithm provides an overview of treating SSRI-induced sexual dysfunction, including impairment of desire, arousal, and orgasm. Specific details are discussed in the UpToDate topic on managing sexual dysfunction caused by SSRIs.

SSRI: selective serotonin reuptake inhibitor.

* A reasonable alternative is switching to an antidepressant that causes less sexual dysfunction, such as bupropion, mirtazapine, or vortioxetine.

¶ Occasionally, an SSRI dose below the usual therapeutic range may be effective and ameliorate sexual dysfunction. A reasonable alternative to lowering the dose is switching to an antidepressant that causes less sexual dysfunction, such as bupropion, mirtazapine, or vortioxetine.

Δ Reasonable alternatives include nonpharmacologic interventions. Refer to the UpToDate topic on managing sexual dysfunction in females.

Graphic 144657 Version 3.0

Hamilton Rating Scale for Depression

1. Depressed mood	
☐	**0** – Absent. **1** – These feeling states indicated only on questioning. **2** – These feeling states spontaneously reported verbally. **3** – Communicates feeling states nonverbally (ie, through facial expression, posture, voice, and tendency to weep). **4** – Subject reports virtually only these feeling states in their spontaneous and nonverbal communication.
2. Feelings of guilt	
☐	**0** – Absent. **1** – Self-reproach, feels they have let people down. **2** – Ideas of guilt or rumination over past errors or sinful deeds. **3** – Present illness is a punishment. Delusions of guilt. **4** – Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.
3. Suicide	
☐	**0** – Absent. **1** – Feels life is not worth living. **2** – Wishes they were dead or any thoughts of possible death to self. **3** – Suicide ideas or gestures. **4** – Attempts at suicide (any serious attempt rates 4).
4. Insomnia – Early	
☐	**0** – No difficulty falling asleep. **1** – Complains of occasional difficulty falling asleep (eg, more than 30 minutes). **2** – Complains of nightly difficulty falling asleep.
5. Insomnia – Middle	
☐	**0** – No difficulty. **1** – Subject complains of being restless and disturbed during the night. **2** – Waking during the night (any getting out of bed rates 2, except for purposes of voiding)
6. Insomnia – Late	

☐	**0** – No difficulty. **1** – Waking in early hours of the morning but goes back to sleep. **2** – Unable to fall asleep again if they get out of bed.

7. Work and activities

☐	**0** – No difficulty. **1** – Thoughts and feelings of incapacity, fatigue, or weakness related to activities, hobbies, or work. **2** – Loss of interest in activities, hobbies, or work, either directly reported by subject or indirect in listlessness, indecision, and vacillation (feels has to push self to work or activities). **3** – Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if subject does not spend at least 3 hours a day in activities (hospital job or hobbies) exclusive o ward chores. **4** – Stopped working because of present illness. In hospital, rate if subject engages in no activities except ward chores, or if subject fails to perform ward chores unassisted.

8. Retardation – Psychomotor

☐	**0** – Normal speech and thought. **1** – Slight retardation at interview. **2** – Obvious retardation at interview. **3** – Interview difficult. **4** – Complete stupor.

9. Agitation

☐	**0** – None. **1** – Fidgetiness. **2** – Playing with hands, hair, etc. **3** – Moving about, can't sit still. **4** – Hand wringing, nail biting, hair pulling, biting of lips.

10. Anxiety – Psychic

☐	**0** – No difficulty. **1** – Subjective tension and irritability. **2** – Worrying about minor matters. **3** – Apprehensive attitude apparent in face or speech. **4** – Fears expressed without questioning.

11. Anxiety – Somatic

☐	**0** – Absent. **1** – Mild. **2** – Moderate. **3** – Severe. **4** – Incapacitating.

12. Somatic symptoms – GI

☐	**0** – None. **1** – Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen. **2** – Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for GI symptoms.

13. Somatic symptoms – General

☐	**0** – None. **1** – Heaviness in limbs, back, or head. Backaches, headaches, or muscle aches. Loss of energy and fatigability. **2** – Any clear-cut symptoms rates 2.

14. Genital symptoms

☐	**0** – Absent. **1** – Mild. **2** – Severe.

15. Hypochondriasis

☐	**0** – Not present. **1** – Self-absorption (bodily). **2** – Preoccupation with health. **3** – Frequent complaints, requests for help, etc. **4** – Hypochondriacal delusions.

16. Loss of weight rated by history

☐	**0** – No weight loss. **1** – Probable weight loss associated with present illness. **2** – Definite (according to subject) weight loss.

17. Insight

☐	**0** – Acknowledges being depressed and ill.

	1 – Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. **2** – Denies being ill at all.

GI: gastrointestinal.

From: Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56.

Graphic 72220 Version 4.0

Education about depression and its initial treatment

What is depression
Depression is a common medical condition that affects the chemistry and functioning of the brain. It can be time limited or, occasionally, become chronic.
Symptoms of depression
Depression can cause emotional symptoms, such as anger, anxiety, and sadness. It can also interfere with memory and concentration and cause physical symptoms, such as fatigue, lack of energy, and agitation. Depression can sometimes cause or worsen existing physical symptoms, such as headache, abdominal or other pain, and muscle tension. Suicidal thoughts and behavior may also occur.
Rationale for treatment
Depression is a treatable medical condition. Antidepressant medications and psychotherapy are evidence-based treatments that improve depression outcomes.
Benefits of antidepressant treatment and psychotherapy include symptom resolution, return to normal function, reduced risk of relapse, and potential improvement in outcomes of other chronic diseases (eg diabetes and cardiovascular disease).
Earlier treatment may be more effective than delayed treatment in achieving remission.
Treatment options
Treatment options for depression include antidepressants, psychotherapy, or both. Exercise can also be effective.
Key points about psychotherapy
Psychotherapy is as effective as antidepressants for treating most cases of depression. Some types of psychotherapy with efficacy for treating depression include cognitive-behavioral therapy, interpersonal therapy, and problem-solving therapy. Therapy can be short term (8 to 16 sessions).
Key points about taking antidepressants
Antidepressants need to be taken every day to work.
Discuss what time of day is best to take the medication and whether to take it with food.
Discuss ways to remember to take the medication.
Give specific instructions on when to increase the dose of the antidepressant. Discuss that most people start with a low dose and then gradually increase the dose to maximize its effectiveness.
Antidepressant side effects
Side effects with antidepressants are common during initial treatment, but many are minor and improve or resolve after the first 2 weeks.
Provide information about common side effects of the prescribed antidepressant.

For SSRIs/SNRIs: Discuss that antidepressants can transiently increase anxiety, agitation, and/or irritability. In young adults, they can occasionally increase suicidal thoughts. If these symptoms are severe or a marked departure from baseline symptoms, the patient should contact their clinician.

Time frame for response to treatment with antidepressants

Symptom improvement can occur as early as 1 to 2 weeks; however, for some patients, a response will require 6 to 12 weeks.

Some patients will not improve after 6 to 12 weeks and may need to try another antidepressant.

Duration of treatment with antidepressants

Patients should continue antidepressant treatment for at least 6 months **after** their symptoms return t baseline. Early discontinuation of antidepressants can increase the risk of relapse.

Tailor duration of antidepressant treatment to the individual patient. Dosing should aim to achieve a maximal, but well-tolerated, dose.

How to discontinue the antidepressant

Abrupt discontinuation of antidepressants occasionally causes withdrawal symptoms, especially in patients who have been taking the antidepressant for many months. Discontinuation symptoms do not indicate addiction or dependence.

Patients taking the antidepressant for more than 2 weeks should taper the dose. The rapidity of taper varies depending on the specific antidepressant and how long the patient has been taking the medication. It should be adjusted if patients develop symptoms during tapering. Patients taking the antidepressant for less than 2 weeks can stop without tapering.

Patients who decide to discontinue their antidepressant should contact their clinician to discuss how to do so.

When to contact the clinician

Patients should contact their clinician if:

- They have more frequent or new onset of thoughts of death or thoughts of hurting themselves or someone else.
- Symptoms or medication side effects are difficult to tolerate, especially worsened anxiety/agitatio or insomnia.
- They stop or are considering stopping depression medication or psychotherapy.
- Symptoms are worsening or not getting better.
- They become pregnant or are considering pregnancy.

Importance of follow-up

Follow-up is the key to the successful treatment of depression. Follow-up allows clinicians to monitor depressive symptoms, response to antidepressant therapy, and side effects. Patients should discuss when and how to follow up with their clinician and schedule regular appointments.

SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

References:

1. *American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd ed, 2010. Available at: https://psychiatryonline.org/guidelines (Accessed on February 27, 2024).*
2. *McCarron RM, Shapiro B, Rawles J, Luo J. Depression. Ann Intern Med 2021; 174:ITC65.*
3. *Dell'Osso B, Albert U, Carrà G, et al. How to improve adherence to antidepressant treatments in patients with major depression: A psychoeducational consensus checklist. Ann Gen Psychiatry 2020; 19:61.*

Graphic 144361 Version 2.0

Toronto Side Effects Scale

Patient name:	**Date:**

Within the last 2 weeks, have you had any of the symptoms listed below?

How much trouble did each symptom cause you?

For each symptom, mark how often (frequency) and how bothersome (severity) it is in the boxes below.

Symptom	**Frequency**					**S**		
	Never 1	**Sometimes 2**	**About half the time 3**	**Often 4**	**Every day 5**	**No trouble 1**	**Some trouble 2**	**M t**
Nervousness	1	2	3	4	5	1	2	
Agitation	1	2	3	4	5	1	2	
Tremor	1	2	3	4	5	1	2	
Twitching/myoclonus (muscle contraction)	1	2	3	4	5	1	2	
Abdominal pain	1	2	3	4	5	1	2	
Dyspepsia (upset stomach)	1	2	3	4	5	1	2	
Nausea	1	2	3	4	5	1	2	
Diarrhea	1	2	3	4	5	1	2	
Constipation	1	2	3	4	5	1	2	
Decreased appetite	1	2	3	4	5	1	2	
Increased appetite	1	2	3	4	5	1	2	
Weakness or fatigue	1	2	3	4	5	1	2	
Dizziness	1	2	3	4	5	1	2	
Postural hypotension (dizzy when getting up)	1	2	3	4	5	1	2	
Drowsiness/daytime somnolence	1	2	3	4	5	1	2	
Increased sleep	1	2	3	4	5	1	2	
Decreased sleep	1	2	3	4	5	1	2	

Sweating	1	2	3	4	5		1	2	
Flushing	1	2	3	4	5		1	2	
Edema (fluid retention)	1	2	3	4	5		1	2	
Headache	1	2	3	4	5		1	2	
Blurred vision	1	2	3	4	5		1	2	
Dry mouth	1	2	3	4	5		1	2	
Anorgasmia/no orgasm	1	2	3	4	5		1	2	
Increased libido	1	2	3	4	5		1	2	
Decreased libido	1	2	3	4	5		1	2	
Other, specify:	1	2	3	4	5		1	2	
Weight gain	None	≤2 lb	≤4 lb	≤6 lb	≤7 lb		1	2	
Weight loss	None	≤2 lb	≤4 lb	≤6 lb	≤7 lb		1	2	
Males only							**Males only**		
Premature ejaculation	1	2	3	4	5		1	2	
Delayed ejaculation	1	2	3	4	5		1	2	
Erectile dysfunction	1	2	3	4	5		1	2	

- **Patient instructions:** Circle the number for frequency and the number for severity that best describes the side effect.
- **Clinician instructions:** An "intensity" score is derived by multiplying frequency score by severity score. Use the intensity score to track the progress of your patient's side effects.

Reproduced with permission from: Vanderkooy JD, Kennedy SH, Bagby RM. Antidepressant side effects in depression patients treated in a naturalistic setting: A study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. Can J Psychiatry 2002; 47:174. Copyright © 2002 Canadian Psychiatric Association.

Graphic 73100 Version 4.0

Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER)

Instructions: Select the best response for the following 3 questions.

1. Choose the response that best describes the frequency (how often) of the side effects of the medication you have taken within the past week for your depression. Do not rate side effects if you believe they are due to treatments that you are taking for medical conditions other than depression. Rate the frequency of these side effects for the past week.

No side effects	Present 10% of the time	Present 25% of the time	Present 50% of the time	Present 75% of the time	Present 90% of the time	Present all of the time
☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6

2. Choose the response that best describes the intensity (how severe) of the side effects that you believe are due to the medication you have taken within the last week for your depression. Rate the intensity of the side effect(s), when they occurred, over the last week.

No side effects	Trivial	Mild	Moderate	Marked	Severe	Intolerable
☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6

3. Choose the response that best describes the degree to which antidepressant medication side effects that you have had over the last week have interfered with your day-to-day functions.

No impairment	Minimal impairment	Mild impairment	Moderate impairment	Marked impairment	Severe impairment	Unable to function
☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6

NOTE: The FIBSER is in the public domain. It may be copied and used without permission.

Reproduced from: Wisniewski SR, Rush AJ, Balasubramani, GK, et al. Self-rated global measure of the frequency, intensity, and burden of side effects. J Psychiatr Pract 2006; 12:71.

Graphic 76881 Version 3.0

Contributor Disclosures

A John Rush, MD Patent Holder: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication [Patent 7,906,283]; Methods to Predict the Outcome of Treatment with Antidepressant Medication [Patent 7,795,033]. Consultant/Advisory Boards: Compass [Psilocybin]; Emmes Corp [Substance use disorder]; Evecxia Therapeutics, Inc [Depression]; Holmusk Technologies, Inc [Depression]; ICON plc [Depression]; Johnson and Johnson [Ketamine]; Liva-Nova [Depression]; MindStreet [Depression]; Neurocrine Biosciences Inc [Depression]; Otsuka-US [Depression]. Speaker's Bureau: Johnson and Johnson [Depression]; Liva-Nova [Depression]. Other Financial Interest: Guilford Press [Royalties]; UT Southwestern [Royalties]. All of the relevant financial relationships listed have been mitigated. **Peter P Roy-Byrne, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Robert McCarron, DO** Consultant/Advisory Boards: Otsuka [Mood disorders]. Speaker's Bureau: Alkermes [Treatment of schizophrenia]. Other Financial Interest: Wolters Kluwer [Royalties for editing psychiatric textbook]. All of the relevant financial relationships listed have been mitigated. **Sara Swenson, MD** No relevant financial relationship(s) with ineligible companies to disclose. **David Solomon, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

