Depression in adults

The right clinical information, right where it's needed

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Summary

- Common symptoms include persistent low mood, loss of interest and enjoyment, sleep and appetite changes, guilt or self-criticism, poor concentration, and reduced energy.

- Affects 5% to 10% of patients in the primary care setting.

- Risk factors include prior depression and a family history of depression. Recent bereavement, stress, or medical illness may contribute.

- For screening and diagnosis, self-rating forms are helpful, but clinical diagnosis is essential. Positive screening should trigger full history, mental status exam, treatment, and follow-up.

- Most patients respond well to treatment with medication, talk therapy, or a combination of both.

- Suicidal ideation can occur before and peak during treatment, so early and careful follow-up is advised.
Definition

Depressive disorders are typically characterized by persistent low mood, loss of interest and enjoyment, neurovegetative disturbance, and reduced energy, causing varying levels of social and occupational dysfunction. Depressive symptoms include depressed mood, anhedonia, weight changes, libido changes, sleep disturbance, psychomotor problems, low energy, excessive guilt, poor concentration, and suicidal ideation. In some cases the mood is not sad, but anxious or irritable or flat.[1]

Major depressive disorder is characterized by the presence of at least five symptoms and can be classified along a spectrum of mild to severe. Severe episodes may include psychotic symptoms such as paranoia, hallucinations, or functional incapacitation.

Subthreshold (minor) depression is characterized by the presence of two to four depressive symptoms, including depressed mood or anhedonia, lasting longer than 2 weeks.

Persistent depressive disorder (dysthymic disorder) is characterized by at least 2 years of three or four dysthymic symptoms for more days than not. Dysthymic symptoms include depressed mood, appetite change, sleep disturbance, low energy, low self-esteem, poor concentration, and hopelessness.

Epidemiology

Depressive disorders are very common and are among the leading causes of disability worldwide.[9] [10] In people aged 18-44 years, depression is the leading cause of disability and premature death. Depression is predicted to be the second leading cause of disability in people of all ages by the year 2020.[11] About 1 in 5 patients in primary care settings had some depressive symptoms between 2005 and 2008. Of these, 10% had depression that was serious enough to warrant pharmacological treatment, but only 33% had received an antidepressant or any treatment from a mental health professional.[12]

About 20% of adults will be affected by a mood disorder needing treatment at some point in their life.[11] Women are affected twice as often as men.[13] In patients with an affected first-degree relative, the lifetime risk of depression increases two- to threefold. First onset occurs most frequently in patients aged 12-24 years or older than 65 years.[11]

Etiology

The etiology of depression remains poorly understood. Integrative models, taking into account biological and social variables, most effectively reflect the complex etiology. There is strong evidence for a genetic component to depression, but specific genetic factors have not been identified.

Gene-environment interaction will probably help explain susceptibility to depression; however, the evidence is mixed. Variants of several genes have been associated with depression in the subset of individuals who have experienced significant life stress.[14] [15] With or without a known genetic component, stressful life events, personality, and sex may also play a modifying role in depression risk.
Pathophysiology

Abnormal concentrations of neurotransmitters, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and abnormalities of second messenger systems have all been identified as being possibly involved in the pathophysiology of depression.

Pathophysiologic theories of monoaminergic neurotransmitters and depression attempt to link the known mechanisms of action of antidepressants to evidence concerning the role of specific neurotransmitters and clinical manifestations of depression. For example, abnormalities in dopamine may be related to impaired motivation and concentration,[16] low levels of norepinephrine and dopamine may play a role in the fatigue and hypersomnia,[17] and impaired norepinephrine and serotonergic regulation may contribute to physical symptoms.[18]

The theory that HPA axis dysregulation is a component of the depressive syndrome is supported by the consistent finding of a failure in individuals with depression of a bedtime bolus dose of the glucocorticoid dexamethasone to inhibit a normal, circadian surge in cortisol the next morning (the dexamethasone suppression test [DST]), along with other suggestive evidence.[19]

Across an analysis of neuroimaging studies from 20 sites internationally, adults with major depression had thinning in regions of the orbitofrontal, cingulate, insular, and temporal cortices,[20] and reduction in hippocampus volume.[21] Structural and functional abnormalities in fronto-limbic networks were also detected in neuroimaging studies of treatment-naive patients with depression.[23]

Classification

Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5)[1]

The Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) divides depression into:

- Major depressive disorder
- Persistent depressive disorder (dysthymia)
- Premenstrual dysphoric disorder
- Other depressive disorders (due to substance abuse, medication side effects, medical conditions, or other specified or unspecified causes).

These types of depression are distinguished based on the length and number of symptoms in addition to sad mood and/or anhedonia, the degree of functional impairment, and the severity of symptoms. Additionally, depressive symptoms as part of cyclothymia or bipolar disorder may also be seen.
**Screening**

**Recommendations**

The US Preventive Services Task Force found convincing evidence to recommend screening for depression in the general adult population, including pregnant and postpartum women,[58] although public health bodies in some countries (e.g., Canada) do not recommend routine screening.[59] Systems should be in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up after screening.

**Tools**

Common screening and diagnostic instruments in present use are based on DSM-IV criteria. DSM-5-based instruments are not yet widely available; however, the symptoms and criteria have changed very little between DSM-IV and DSM-5, so no significant changes in the screening instruments are anticipated.

The Patient Health Questionnaire-2 (PHQ-2) is derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD) tool and quickly and accurately screens for depression with only 2 questions:[43]

"Over the past 2 weeks have you felt down, depressed, hopeless?"

"Over the past 2 weeks have you felt little interest or pleasure in doing things?"

A positive response to either question warrants a thorough review of the DSM-5 criteria or an equivalent tool.

The Patient Health Questionnaire-9 (PHQ-9) can be used as a diagnostic and disease management tool. The PHQ-9 is a 9-item depression questionnaire that reflects the DSM-5 criteria. It classifies current symptoms on a scale of 0 (no symptoms) to 3 (daily symptoms). It has been validated for use in primary care settings. Repeating the PHQ-9 during treatment allows the clinician to objectively monitor response to therapy.

**Screening pregnant and postpartum women**

Evidence suggests that screening pregnant and postpartum women reduces the risk of depression.[3] [4] [58] Clinicians should screen for postpartum depression using the Edinburgh Postnatal Depression Scale 4 to 6 weeks after delivery. [Edinburgh Postnatal Depression Scale] This scale is a 10-item questionnaire for postpartum women. A score of ≥10 suggests depression.[44] [45] [46] Although it does not assess the severity of depression, it does assess for suicidal ideation.

**Secondary prevention**

Patients and their families must be cautious during the early stages of medication treatment, as the risk of suicide may temporarily increase.
Case history

Case history #1

A 45-year-old woman presents with a one-month history of poor sleep and irritable mood, in the setting of a recent divorce and ongoing custody battle with her former husband over their 2 teenage children. She has also just had a bad performance review at work due to her inability to meet deadlines and is fearful of losing her job. She explains that her work problems have arisen because she has been unable to keep her concentration focused on work. She expresses feelings of worthlessness and wonders sometimes what is the point of living. She has to force herself to stay engaged in her children’s activities and other interests that she used to enjoy; she feels she is “just going through the motions”. She had a similar episode after the birth of her second child, but pulled out of it after several months. There is a family history of suicide; her mother killed herself when the patient was 10 years old. Her exam is notable for poor eye contact and frequent tears. Her test results, including the thyroid-stimulating hormone, are normal.

Other presentations

In older people, depression can present as diminished self-care, psychomotor retardation, irritability, and apathy. These patients may also present with severe cognitive disturbance (memory deficits) as a result of the depression. Several diagnostic tools are available for this population, such as the Geriatric Depression Scale,

[VIDEO: Geriatric Depression Scale ]
and, when cognitive impairment is prominent, the Cornell Scale for Depression in Dementia.  [Cornell Scale For Depression in Dementia]

Women in the postpartum period are at high risk for depression.[2] Evidence suggests that screening pregnant and postpartum women reduces the risk of depression.[3] [4] Clinicians should be vigilant in pregnancy and the weeks after delivery, and may screen for postpartum depression using the Edinburgh Postnatal Depression Scale.  [Edinburgh Postnatal Depression Scale]

Patients with diabetes, cancer, stroke, myocardial infarction, obesity, and other general medical conditions have significantly higher rates of depression than people without comorbid conditions and may present atypically with nonadherence, multiple unexplained symptoms, or chronic pain syndromes.[5] [6] [7] [8]

Step-by-step diagnostic approach

History

Patients may present with a history of depressed, anxious, irritable, or flat mood, anhedonia, weight changes, libido changes, sleep disturbance, psychomotor problems, low energy, excessive guilt, poor concentration, or suicidal ideation.[1] Patients often have a personal or family history of depression. Some, but certainly not all, will have experienced a recent stress, trauma, or loss, or have comorbid medical illness. In older patients, depression can present as diminished self-care, psychomotor
retardation, irritability, and apathy. These patients may also present with severe cognitive disturbance (memory deficits) as a result of the depression.

**Exam**

There are no definitive findings of depression on physical exam, although most patients will have a depressed affect, as well as a downcast gaze, furrowed brow, psychomotor slowing, speech latency, and expressions of guilt or self-blame. The physical exam and cognitive screening may be useful in ruling out common conditions that are often confused with depression (e.g., hypothyroidism, dementia) and in looking for commonly co-occurring illnesses (including obesity, cancer, stroke).

**Depression screening**

Commonly used screening tests include the Primary Care Evaluation of Mental Disorders (PRIME-MD) and 9-item Depression Scale of the Patient Health Questionnaire (PHQ-9) for adults in primary care[40] and the Edinburgh Depression Score for Postpartum Depressions. [Edinburgh Postnatal Depression Scale] The US Preventive Services Task Force recommends that primary care practices screening adults should have systems in place that ensure positive screening results are followed by accurate diagnosis, effective treatment, and careful follow-up.[41]

**Depression diagnosis**

To ensure diagnostic accuracy, physicians should apply DSM-5 criteria to all patients suspected of having depression or who have a positive screening test for depression. Determining whether the episode is mild, moderate, or severe, with or without psychosis, informs treatment decisions.

  • Criteria for major depression: according to DSM-5, is five or more depressive symptoms, including depressed mood or anhedonia, for at least 2 weeks.[1]

For patients with dementia who might not readily be able to recognize or describe symptoms due to cognitive impairment, clinical assessment is essential in case finding, and can be supported by the use of a variety of diagnostic tools.[42] Specific structured diagnostic assessments for older people are available and should be used instead of the PRIME-MD or PHQ-9: for example, the Geriatric Depression Scale, [VIDEO: Geriatric Depression Scale ] or for older people with cognitive impairment, the Cornell Scale for Depression in Dementia. [Cornell Scale For Depression in Dementia] Physicians can use the PHQ-9 to score current depression severity and to follow up treatment response.

**Tests**

Simple laboratory tests should be performed in the workup to exclude other causes of depression symptoms. Initial tests include thyroid function tests, metabolic panel, and complete blood count. Serum vitamin B12 and folate levels, and 24-hour urinary cortisol may also be informative (and, if elevated, is suggestive of Cushing disease).

**Risk factors**

**Strong**
Depression in adults

**Diagnosis**

**age >65 years**
- The prevalence of depression in medical outpatients older than age 65 years ranges from 7% to 36%, depending on the setting. Up to 50% of patients with Alzheimer disease and Parkinson disease develop a depressive disorder; their caregivers, regardless of age, are also at increased risk.[25]

**postpartum status**
- About 19% of postpartum women have a major depressive episode during the first 3 months after delivery.[26] Women with a previous psychiatric disturbance, poor social support, and an unplanned pregnancy are at higher risk.[2] Parenting programs may improve the short-term psychosocial health of mothers.[27]

**personal or family history of depressive disorder or suicide**
- A family history of depression is associated with a twofold increased risk, more functional impairment, longer episodes, more frequent recurrence, and persistent thoughts of death and suicide.[28] The rate of suicide is twice as high in families of suicide victims.[29]

**corticosteroids**
- Depression is a documented adverse effect.

**interferon**
- Depression is a documented adverse effect and is treatable.[30]

**propranolol**
- Depression is a documented adverse effect.

**oral contraceptives**
- Depression is a documented adverse effect.

**coexisting medical conditions**
- Patients with various chronic medical conditions, including diabetes, cancer, stroke, coronary artery disease, HIV, chronic pain, polycystic ovary syndrome, and obesity have significantly higher rates of depression than people without comorbidities.[5] [6] [7] [8] [31] [32] [33] [34] Moreover, the relationship is bidirectional. Depressed patients are more likely to develop chronic medical conditions.[35] [36] Adults who experienced chronic medical illness in childhood also have higher rates of depression.[37]

**Weak**

**isotretinoin**
- Depression is a documented rare adverse effect.

**comorbid substance use**
- Depressed patients may abuse drugs to “dull the pain” or to address feelings of low self-worth. Additionally, the chemical effects of drug use may cause depressed mood.
personality disorders

- Some personality disorders co-occur more frequently with depression. Depression combined with a personality disorder may have a poorer outcome than depression alone; however, data are mixed.[38]

gene-environment interaction

- It is unclear whether a gene environment interaction can help explain susceptibility to depression. One meta-analysis published in 2009 supported the previous finding that stressful life events have a potent relationship with the risk of depression, but yielded no evidence that the serotonin transporter genotype alone or in interaction with stressful life events is associated with a higher risk of depression in either men or women.[39] However, one 2018 meta-analysis of FKBP5 gene variants interacting with early life stress suggested a gene-environment risk factor for depression.[15]

History & examination factors

Key diagnostic factors

depressed mood (common)

- According to DSM-5, major criterion for diagnosis: depressed mood most of the day, nearly every day, for a period of 2 weeks along with 4 other symptoms of depression.[1]

anhedonia (common)

- According to DSM-5, major criterion for diagnosis: diminished interest or pleasure in all or almost all activities most of the day, nearly every day, for a period of 2 weeks along with 4 other symptoms of depression.[1]

functional impairment (common)

- According to DSM-5, symptoms cause impairment in, for example, social or occupational functions.[1]

Other diagnostic factors

weight change (common)

- According to DSM-5, significant weight loss when not dieting, weight gain, or decrease or increase in appetite nearly every day.[1]

libido changes (common)

- May show reduced libido.

sleep disturbance (common)

- According to DSM-5, insomnia or hypersomnia nearly every day.[1]

psychomotor problems (common)

- According to DSM-5, psychomotor agitation or retardation nearly every day.[1]

low energy (common)

- According to DSM-5, fatigue or loss of energy nearly every day.[1]

excessive guilt (common)
Depression in adults

Diagnosis

- According to DSM-5, feelings of worthlessness or excessive or inappropriate guilt nearly every day.[1]

**poor concentration (common)**
- According to DSM-5, diminished ability to think or concentrate nearly every day.[1]

**suicidal ideation (common)**
- According to DSM-5, recurrent thoughts of death, recurrent suicidal ideation without a specific plan.[1]

**bipolar disorder excluded (common)**
- According to DSM-5, there should be no evidence of mania or hypomania.[1]

**substance abuse/medication side effects excluded (common)**
- According to DSM-5, major depressive disorder should not be diagnosed if the symptoms are primarily attributable to the pharmacologic effects or side effects of prescribed medications or substances of abuse.[1]

**medical illness excluded (common)**
- According to DSM-5, major depressive disorder should not be diagnosed if the symptoms are primarily attributable to a somatic medical condition.[1]

**schizophrenia excluded (uncommon)**
- According to DSM-5, chronic psychosis excludes the diagnosis of major depressive disorder if the depressive symptoms are primarily attributable to the chronic psychotic illness.[1]
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>clinical diagnosis</strong></td>
<td>DSM-5 diagnostic criteria depending on the depressive subcategory</td>
</tr>
</tbody>
</table>
| • Major depression:  
  ≥5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure: depressed mood most of the day, nearly every day as self-reported or observed by others; diminished interest or pleasure in all or almost all activities most of the day, nearly every day; significant weight loss when not dieting, weight gain or decrease or increase in appetite nearly every day; insomnia or hypersomnia nearly every day; psychomotor agitation or retardation nearly every day; fatigue or loss of energy nearly every day; feelings of worthlessness or excessive or inappropriate guilt nearly every day; diminished ability to think or concentrate nearly every day; recurrent thoughts of death, recurrent suicidal ideation without a specific plan.  
  • In addition, these symptoms: cause functional impairment (e.g., social, occupational); are not related to substance abuse, medication side effects, or another medical condition; are not related to a grief reaction.  
  • Women who have clinically significant changes in mood along with other depressive symptoms, linked to the menstrual cycle, may warrant a diagnosis of premenstrual dysphoria. Patients who have depressive symptoms attributable to another cause, such as psychoactive drugs, medication side effects, or medical illness, may be diagnosed with specific substance-induced or medication-related depressive symptoms or depression secondary to a specified somatic medical condition, respectively. Otherwise, clinically significant depression where the symptoms fall short of meeting full DSM criteria in number, duration, or severity can be diagnosed as either "other specified depressive disorder" (where the reason for falling short of criteria is given: for example, "brief" or "short-duration" or "insufficient symptoms") or "unspecified depressive disorder" where the reason is not stated.  
  • Persistent depressive disorder: the patient has a major depressive syndrome for ≥2 years, or ≥3 dysthymic symptoms, including depressed mood, for ≥2 years (>1 year in children and adolescents). Dysthymic symptoms are as follows: depressed mood, appetite changes, sleep changes, low self-esteem, fatigue, poor concentration, and hopelessness. |
<p>| <strong>metabolic panel</strong>          | normal                                      |
| • Provides baseline and may reveal metabolic disturbance. |
| <strong>CBC</strong>                     | normal                                      |
| • Other causes of fatigue such as anemia should be ruled out. |
| <strong>thyroid function tests</strong>  | normal                                      |
| • An elevated serum thyroid-stimulating hormone level suggests hypothyroidism. |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Health Questionnaire-2 (PHQ-2)</strong></td>
<td>positive result screens for depression in primary care</td>
</tr>
<tr>
<td>• The PHQ-2</td>
<td><img src="#" alt="VIDEO: Depression (any) Screening by a Two Item PHQ-2" /></td>
</tr>
<tr>
<td>is derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD) tool and quickly and accurately screens for depression with only two questions: Over the past 2 weeks, have you felt down, depressed, hopeless? and over the past 2 weeks, have you felt little interest or pleasure in doing things?</td>
<td></td>
</tr>
<tr>
<td>• A positive response to either question warrants a thorough review of the DSM-5 criteria or an equivalent tool.</td>
<td><img src="#" alt="DIAGNOSIS" /></td>
</tr>
<tr>
<td><strong>Patient Health Questionnaire-9 (PHQ-9)</strong></td>
<td>positive result screens for depression in primary care</td>
</tr>
<tr>
<td>• The PHQ-9 can be used as a diagnostic and disease management tool.</td>
<td><img src="#" alt="VIDEO: Depression (any) Screening by a Two Item PHQ-2" /></td>
</tr>
<tr>
<td>The PHQ-9 is a 9-item depression questionnaire that reflects the DSM-5 criteria. It classifies current symptoms on a scale of 0 (no symptoms) to 4 (daily symptoms). It has been validated for use in primary care settings. Repeating the PHQ-9 during treatment allows the clinician to objectively monitor response to therapy.</td>
<td><img src="#" alt="DIAGNOSIS" /></td>
</tr>
<tr>
<td><strong>Edinburgh Postnatal Depression Scale</strong></td>
<td>positive result screens for depression in postpartum period</td>
</tr>
<tr>
<td>• Clinicians should screen for postpartum depression using the Edinburgh Postnatal Depression Scale 4-6 weeks after delivery.</td>
<td><img src="#" alt="Edinburgh Postnatal Depression Scale" /></td>
</tr>
<tr>
<td>This scale is a 10-item questionnaire for postpartum women. A score of ≥10 suggests depression; however, clinicians should be mindful of individual patient circumstances (e.g., education and culture) that might impact scoring. Although it does not assess the severity of depression, it does assess for suicidal ideation.</td>
<td><img src="#" alt="DIAGNOSIS" /></td>
</tr>
<tr>
<td><strong>Geriatric Depression Scale</strong></td>
<td>&gt;5 suggests depression; &gt;10 strongly suggests depression</td>
</tr>
<tr>
<td>• The short form contains 15 yes/no questions.</td>
<td><img src="#" alt="VIDEO: Geriatric Depression Scale" /></td>
</tr>
<tr>
<td>• This scale does not assess the severity of symptoms.</td>
<td><img src="#" alt="DIAGNOSIS" /></td>
</tr>
<tr>
<td><strong>Cornell Scale for Depression in Dementia</strong></td>
<td>&gt;10 suggests probable depression; &gt;18 indicates definite depression</td>
</tr>
<tr>
<td>• This scale is a 19-item questionnaire intended for geriatric patients with dementia.</td>
<td><img src="#" alt="Cornell Scale For Depression in Dementia" /></td>
</tr>
<tr>
<td>• This scale does not assess the severity of symptoms.</td>
<td><img src="#" alt="DIAGNOSIS" /></td>
</tr>
</tbody>
</table>
# Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour free cortisol</td>
<td>normal</td>
</tr>
<tr>
<td>• Elevated 24-hour urinary free cortisol level suggests Cushing disease.</td>
<td></td>
</tr>
<tr>
<td>vitamin B12</td>
<td>normal</td>
</tr>
<tr>
<td>• Vitamin B12 deficiency is associated with macrocytic anemia, paresthesia, numbness, and impaired memory.</td>
<td></td>
</tr>
<tr>
<td>folic acid</td>
<td>normal</td>
</tr>
<tr>
<td>• Patients with depression have been found to have lower levels of serum folate than normal or nondepressed psychiatric patients.[50]</td>
<td></td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustment disorder with depressed mood</td>
<td>• This is a subsyndromal depression with a clearly identified precipitating event. It usually does not require medication and resolves with resolution of the acute stressor.</td>
<td>• DSM-5.</td>
</tr>
<tr>
<td>Substance/medication- or medical illness- associated and other depressive disorders</td>
<td>• Depressive symptoms that fall short of diagnostic criteria for major depressive disorder due to concurrent substance use, medication side effects, or somatic medical illness, or for other specifiable or unspecifiable reasons.</td>
<td>• Medical history and physical, chemistry, hematological, and other tests to rule out or diagnose somatic medical illness; review and monitoring of prescription drugs for possible side effects; toxicology screen for evidence of substance abuse.</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>• In this condition, major depressive disorder is accompanied by or interspersed with one or more manic, hypomanic, or mixed episodes.</td>
<td>• DSM-5.</td>
</tr>
<tr>
<td>Premenstrual dysphoric disorder (PMDD)</td>
<td>• PMDD is characterized by depressed mood, anxiety, and irritability during the week before menses and resolving with menses. PMDD also has prominent pain symptoms.</td>
<td>• DSM-5.</td>
</tr>
<tr>
<td>Grief reaction</td>
<td>• Depressive symptoms may be transiently present in normal grief. The duration and expression of normal grief varies among racial/ethnic groups.[51] • Symptoms more consistent with depression include inappropriate guilt regarding actions surrounding death of loved one, persistent thoughts of death (survivor’s feelings that he or she would be better off dead or should have died with the deceased person are considered a normal part of grief), morbid preoccupation</td>
<td>• DSM-5.</td>
</tr>
</tbody>
</table>
## Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Depression in adults | with worthlessness, marked psychomotor retardation, prolonged and marked functional impairment, and hallucinations. Transiently hearing the voice of or seeing the deceased person is considered within normal limits of bereavement. 
- According to DSM-5, if the patient has a full syndrome of major depressive disorder, a recent loss or state of bereavement does not preclude the diagnosis or preclude the benefits of antidepressant treatment. However, a psychotherapeutic approach aimed at bereavement is likely to be more successful than standard psychotherapeutic approaches for depression. | |
| Dementia       | • Dementia is characterized by cognitive (memory) changes, psychiatric symptoms, personality changes, problem behaviors, and changes in day-to-day functioning. | • A mini-mental state exam or neuropsychiatric testing should be conducted if the diagnosis is uncertain. 
- Focused laboratory testing (i.e., thyroid-stimulating hormone level, vitamin B12 level) should be considered for reversible causes of dementia. |
| Anxiety disorders | • Anxiety disorders frequently occur along with depression. Generalized anxiety disorder (GAD) is characterized by excessive worry, muscular tension, fatigue, autonomic hyperactivity, and increased vigilance; patients with anxious depression may appear to have GAD. Specific anxiety disorders (i.e., panic disorder, social phobia, obsessive-compulsive disorder, PTSD) should also be considered. | • DSM-5. |
| Alcohol abuse  | • Patients often may complain of insomnia,                                                                                                             | • Various screening tools are in wide use, including the CAGE questionnaire |
### Condition Differentiating signs / symptoms Differentiating tests

<table>
<thead>
<tr>
<th>Condition</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression in adults</td>
<td>Nightmares, poor memory, and nervousness.</td>
<td>and the Alcohol Use Disorders Identification Test (AUDIT).[55]</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>• Eating disorders such as anorexia nervosa are more common in women and characterized by disturbance in the perception of body weight, size, or shape, and refusal to maintain healthy body weight.</td>
<td>• DSM-5.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>• Associated signs and symptoms include weight gain, constipation, and fatigue.</td>
<td>• An elevated serum thyroid-stimulating hormone level suggests hypothyroidism.</td>
</tr>
<tr>
<td>Medication adverse effects</td>
<td>• Patient should be asked about use of glucocorticoids, interferon, levodopa, propranolol, and oral contraceptives. The data regarding isotretinoin remain unclear.[56]</td>
<td>• These effects may be temporally associated with medication initiation.</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>• This disease is associated with progressive obesity, dermatologic manifestations, signs of adrenal androgen excess, and proximal muscle wasting.</td>
<td>• Elevated 24-hour urinary free cortisol level.</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>• This deficiency is associated with macrocytic anemia, paresthesia, numbness, and impaired memory.</td>
<td>• Reduced serum vitamin B12 level.</td>
</tr>
<tr>
<td>Obstructive sleep apnea (OSA)</td>
<td>• Depressive symptoms are a common consequence of OSA, and can be reversed by treatment directed at the OSA.[57]</td>
<td>• Sleep study.</td>
</tr>
</tbody>
</table>

## Diagnostic criteria

### Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5)[1]

The Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) divides depression into:

- Major depressive disorder
- Persistent depressive disorder (dysthymia)
Depression in adults

**Depression in adults**

**Diagnosis**

- Premenstrual dysphoric disorder
- Other depressive disorders (not meeting major depressive disorder criteria due to substance abuse, medication side effects, medical conditions, or other specified or unspecified reasons).

## Major depression[1]

Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure:

- Depressed mood most of the day, nearly every day, as self-reported or observed by others
- Diminished interest or pleasure in all or almost all activities most of the day, nearly every day
- Significant weight loss when not dieting, weight gain, or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan.

In addition, these symptoms:

- Cause functional impairment (e.g., social, occupational)
- Are not better explained by substance abuse, medication side effects, or other psychiatric or somatic medical conditions.

There are 3 degrees of severity of major depression defined in the DSM-5:

- Mild: few if any symptoms more than number required for diagnosis of major depression with minor functional impairment
- Moderate: more than required number of symptoms for diagnosis of depression with greater intensity and moderate impairment in functioning
- Severe: many more symptoms than required for diagnosis of depression with intense functional impairment; psychotic features such as hallucinations or paranoia may be present.

## Depressive disorder (subthreshold or minor depression)[1]

This diagnostic designation does not exist in DSM-5, but when used in the past it referred to a patient who had from 2 to 4 depressive symptoms, including either sad mood or anhedonia for at least 2 weeks.

## Depressive disorder due to:

- Substance/medication use/abuse: full or partial major depressive syndrome attributable to pharmaceuticals or other intoxicants
- Medical condition: full or partial major depressive syndrome attributable to another somatic medical illness
• Other (specified or unspecified) depressive disorder: major depressive syndrome attributable to another external or somatic cause, or a depressive syndrome that for other known or unknown reasons falls short of a full major depressive syndrome.

Persistent depressive disorder[1]

This diagnosis encompasses and expands the now-unused diagnosis "dysthymic disorder". The patient has a major depressive syndrome or 3 or 4 dysthymic symptoms, including depressed mood, for ≥2 years. Impairment compared with major depressive disorder may be less severe. Dysthymic symptoms are as follows:

• Depressed mood
• Appetite changes
• Sleep changes
• Low self-esteem
• Fatigue
• Poor concentration
• Hopelessness.
Step-by-step treatment approach

The goals of treatment are to eradicate symptoms of depression, improve daily functioning and quality of life, improve workplace functioning, reduce suicidality, minimize treatment adverse effects, and prevent relapse. Treatment modalities include antidepressants, other pharmacotherapies, psychotherapies, supportive interventions, and electroconvulsive therapy (ECT). For patients with depression undergoing outpatient treatment, significant benefits are associated with the collaborative chronic care model that incorporates patient training, organizational support, community resources, and other multidisciplinary interventions. Collaborative care appears to be effective both for patients with depression alone and for those with depression and comorbid chronic physical conditions. Issues yet to be resolved in the effective deployment of collaborative care models include the education of providers, reimbursement, and communication. The use of internet- and mobile-based interventions have also been shown to reduce depressive symptoms.

Severe depression

Patients with severe depression include those who are psychotic, suicidal, catatonic, or have severe psychomotor retardation impeding activities of daily living, or severe agitation. These patients are at increased risk for suicide, impulsive and potentially self-destructive behavior, and health complications due to poor self-care and immobility.

Specialist referral, hospitalization, constant observation, tranquilization, and/or ECT may be required to keep the patient safe until definitive antidepressant therapy can take effect. The pharmacologic and nonpharmacologic treatment options used in these patients, once the risks have been stabilized, are discussed in the section on "Moderate depression" (below).

Specialist referral is indicated and hospitalization should be considered if patients:

- Have significant suicidal ideation or intent and lack adequate safeguards in their family environment
- Have intent to hurt others
- Are unable to care for themselves and adhere to their treatment
- Have psychotic symptoms
- Have uncontrolled agitation accompanied by the risk of impulsive behavior.

Suicide risk management

- Suicide risk assessment is critical, especially as the risk may increase early in treatment. Routinely asking patients about suicidal ideation and reducing access to lethal means (especially firearms) can reduce the risk of suicide. Close telephone follow-up by a trained psychiatrist may help reduce the risk of death by suicide after a previous suicide attempt.

Pharmacotherapy

- General principles of prescribing antidepressants are described in the section below on "Moderate depression". Antidepressants alone may not effectively address psychotic symptoms, such as delusions or hallucinations; therefore, clinicians should have a lower threshold for adding an antipsychotic to antidepressant treatment in severe cases under several circumstances.
- For patients who have agitation as a depressive symptom, antipsychotics can directly tranquilize the distress associated with this form of severe depression. Agitated patients may require...
symptomatic treatment with a benzodiazepine, or possibly both an antipsychotic and a benzodiazepine, until definitive antidepressant therapy takes effect.

Electroconvulsive therapy (ECT)

- Although most patients referred for ECT have tried other antidepressant treatments, ECT may be considered as first-line treatment in certain patients with severe depression. It may be used early in treatment for psychosis, suicidality, or catatonia, or later in treatment for people with refractory depression or intolerance to antidepressants. ECT is often the treatment of choice for severely depressed older patients; it is effective,[75] and avoids complications that may arise from pharmacologic intolerance and drug interactions associated with treatment for comorbid physical conditions.

- ECT is performed under general anesthesia, 2 or 3 times a week for a total of 6 to 12 treatments.

- Patient and clinician must be fully informed of the potential risks, so that the patient can provide informed consent. The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments,[76][77] meaning that it is one of the safer procedures performed under general anesthetic. The risk of death may be increased in patients with coronary heart disease, due to a theoretical increased risk of ischemia during the induced seizure. According to one systematic review, the majority of patients report adverse cognitive effects during and shortly after treatment, most commonly memory loss (both anterograde and retrograde amnesia).[78] This impairment seems to be short-lived according to objective assessment,[79] although a significant proportion of patients report persistent memory loss following ECT.[78] This potential risk must be balanced against the evidence in favor of its efficacy, especially in patients with severe depression.

Supportive care

- Agitated patients require high levels of care because of their enhanced emotional distress and the risk of impulsive violence. Severe impairment of the activities of daily living due to catatonia or psychomotor retardation increases the severity of depression, as patients who are inert and bedbound, or not taking adequate sustenance run the risk of a deterioration in health while awaiting a response to pharmacotherapy. These patients may require supportive nursing care.

Psychotherapy

- Patients with severe depression are unlikely to find other talking treatment effective, and it may worsen their outlook. Limit psychotherapy to the support necessary to manage the patient safely and to encourage the patient to accept definitive treatment.

**Moderate depression**

Patients with moderate depression have severe symptoms, significant impairment but no psychotic symptoms, no suicidal ideation, and no severe psychomotor retardation or agitation. These patients are suffering and if not unable to perform their normal life tasks, they are finding it very difficult to do so.

Antidepressants are necessary in these patients,[80][81][82] but are possibly not sufficient to improve patient outcomes. Moderately to severely depressed patients derive the greatest benefit from the combination of antidepressants and psychotherapy.[83][B]Evidence Close follow-up and at minimum supportive or educational interventions during the onset of treatment can improve medication adherence.
They may also reduce the risk of self-injury or suicide that can emerge in the very early phases of recovery, when energy and arousal have increased but mood remains depressed.

General principles of antidepressant treatment

- The main antidepressant options include:
  - selective serotonin-reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline);
  - serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine);
  - bupropion (a dopamine-reuptake inhibitor);
  - mirtazapine (a 5-HT2 receptor antagonist);
  - vilazodone (an SSRI and partial 5-HT1A receptor agonist); and
  - vortioxetine (a serotonin-reuptake inhibitor with serotonin receptor modulation properties).

- Selection of an antidepressant depends on factors other than the relative efficacy of different agents; no consistent differences in safety or efficacy have been demonstrated between antidepressants,[84] although some head-to-head differences between drugs in relation to their efficacy and acceptability have been revealed in one large meta-analysis, and might be considered as one of many factors to consider in treatment selection.[82] According to one different meta-analysis of individual patient data from 15 controlled trials of acute-phase treatment of major depression, mirtazapine may be a more rapidly effective antidepressant than SSRIs.[85]

- Choice of drug should be based on patient preference, tolerability, and past evidence of effectiveness in the patient. Some clinicians may also have a lower threshold for considering treatment with an antidepressant that has been shown to be effective in a family member. One rationale for this is that a person who has seen a family member respond to a particular drug may find treatment with this drug more acceptable and may have increased expectations for recovery. This is, however, not an evidence-based approach; advances in pharmacogenomics (examining the impact of heritable genetic factors on treatment efficacy and tolerability for individual patients) may eventually provide clarification, but pharmacogenomic analysis is not yet recommended for routine use.[86]

- Although the net result of antidepressant response is a significant reduction in suicidal ideation,[80][87] there is some evidence of increased suicidal behavior in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[88][89] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.[90][91] The results of one large meta-analysis suggest that in adults under the age of 25, the risk of both emergence and worsening of suicidality may be raised in weeks 3-6 of treatment (but not in weeks 1-2), which is later than has been suggested by other studies.[92]

- Follow up patients 1 to 2 weeks after initiating therapy, then monthly for the next 12 weeks. If you prefer systematic evaluation, use the Patient Health Questionnaire-9 (PHQ-9) to assess changes in symptom severity. Titrate the antidepressant dose to the maximum tolerated in patients who experience a partial response after 2 to 4 weeks. Patients are likely to begin to show a response within the first 1 to 2 weeks of treatment; however, successful antidepressant therapy to the point of
remission of all symptoms may take 6 to 8 weeks. A 50% decrease in symptom score constitutes an adequate response, and a 25% to 50% change in symptom score may indicate the need to modify treatment.

- Determine antidepressant dose based on the known target dose range. In a minority of patients, pharmacogenomic testing may indicate using a low-end or high-end dose depending on genotype. On balance, there is no evidence to support routinely increasing the dose beyond the established dose range.[93]

- If the response to first-line therapy is inadequate, consider switching to an alternative antidepressant.[94] [95] By the end of 4 different medication trials, 60% to 70% of patients are likely to respond to treatment. Switching may be appropriate if no improvement in symptoms has occurred within the first 2 weeks of treatment.[96] [97] however, be aware that early response may be, but is not necessarily, a reliable indicator of continued response.[98] [99] Continue treatment if there has been some improvement for at least the full 6 to 8 weeks, but do not continue prescribing a drug providing inadequate benefit indefinitely. Of note, in patients with no initial improvement to treatment with fluoxetine, one study showed the likelihood of converting to a positive response decreased the longer patients remained unimproved.[100]

- Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. The timeframe required for safely switching depends on various factors including the pharmacokinetic properties of the drugs and possible interactions between them, as well as patient characteristics such as age, sensitivity to adverse effects, and the capacity to wait to begin a new course of treatment. In some situations, it is possible to give both drugs for a short period of time while the changeover is occurring; however, this should only be done under specialist guidance. In other cases, it is safer to take a more conservative approach. This involves slowly tapering the dose of the first drug before stopping it, and then waiting a period of time before starting the second drug (known as a washout period, which is usually five half-lives of the first drug). Drugs with longer half-lives (e.g., fluoxetine) require longer washout periods (e.g., up to 5 to 6 weeks) when combined with a drug with which the combination is contraindicated (e.g., monoamine oxidase inhibitors with fluoxetine). Specific recommendations for switching from one antidepressant to another, along with suitable washout periods, are available and local guidance should be consulted. When in doubt, in the absence of such guidelines, as a general principle perform a drug interaction check to be sure there are no absolute contraindications, and then "start low and go slow" until safety can be ascertained.

- If there is an inadequate response to 2 (or more) full-dose and duration antidepressants, the patient’s depression might be considered treatment resistant or refractory, and warrants a more complex approach, as outlined in the "Treatment-resistant/refractory depression" section below.

- Duration of treatment following the remission of symptoms depends on the prior course of illness. Evidence shows reduced risk of relapse when antidepressants are continued for over 6 months.[101] [102] [103] 2[A]Evidence Continue successful antidepressant treatment for 9 to 12 months following remission.[102] [103] 2[A]Evidence Continue maintenance treatment indefinitely if the patient has had multiple episodes and relapses, incomplete treatment response, or complicating problems, such as substance abuse, that might tend to promote recurrence.[104]

Psychotherapy and other nonpharmacologic treatments

- Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[105] [106]
• In addition to pharmacotherapeutic strategies, cognitive behavioral therapy (CBT) has shown greater efficacy than pharmacologic placebo across levels of severity.[107] Treatment response to CBT is comparable with antidepressant response in some studies.[108] Staged treatment trials suggest that CBT may be particularly beneficial when used during the continuation phase of treatment; CBT reduces the risk of relapse/recurrence at least as well as, and perhaps better than, antidepressant continuation.[109] [110] [111] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[112] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[113]

• Therapists often use a combination of CBT[114] and interpersonal psychotherapy (IPT)[114] or problem-solving therapy (PST).[115] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[117] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[118] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. PST focuses on training in adaptive problem-solving attitudes and skills.[115] [119]

• Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[120]

• Behavioral activation is a less cerebral, more behavioral alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomized controlled trial found it to be no less effective than CBT for adults with depression.[121]

• ECT may be an option for those who have not responded to, or cannot tolerate, antidepressants; the response rate is better for patients with severe major depression than for moderate or mild depression.

Mild depression

Patients with mild depression have low to moderate severity symptoms, partial impairment, no psychotic symptoms, no suicidal ideation, and no psychomotor retardation or agitation.

These patients do equally well with either CBT[122] or an antidepressant.[122] Combination psychotherapy and medication offers no demonstrated short-term advantage in this group. However, continued psychotherapy with antidepressant management is an effective option when continued through both acute and ongoing phases of treatment.[83]

The initial choice of therapy should be guided by patient preference and includes:

• Antidepressant treatment
• Psychotherapy[123] [124] [125]
• Supportive interventions: self-help books, yoga, relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture[126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [136] [137] [138] [139] [140] and
• Computer-based treatment: CBT,[141] [142] [143] [144] [145] [146] PST,[147] [148] and stress management.[149]

Antidepressant treatment
• An antidepressant may be preferable in some patients as it may offer a more rapid response than nonpharmacologic therapies. The most commonly prescribed antidepressants, SSRIs and SNRIs, offer similar response rates and can be used first line as monotherapy in mild to moderate disease. There is essentially no consistent evidence that any of the traditional antidepressants are superior to any other.

• Choice of drug should be based on patient preference, tolerability, and past evidence of effectiveness in the patient. Some clinicians may also have a lower threshold for considering treatment with an antidepressant that has been shown to be effective in a family member. One rationale for this is that a person who has seen a family member respond to a particular drug may find treatment with this drug more acceptable and may have increased expectations for recovery. This is, however, not an evidence-based approach; advances in pharmacogenomics (examining the impact of heritable genetic factors on treatment efficacy and tolerability for individual patients) may eventually provide clarification.

• Follow up patients 1 to 2 weeks after initiating therapy, then monthly for the next 12 weeks. Use the PHQ-9 to monitor symptoms over time. Patients who experience a partial response to antidepressants after 2 to 4 weeks should have the dose titrated to the maximum tolerated. Continue successful antidepressant treatment for 9 to 12 months following remission; however, some physicians recommend indefinite therapy for patients with frequent previous recurrences and relapses, and who respond successfully to antidepressant treatment.

Psychotherapy

• Psychotherapy is also considered a first-line option in mild to moderate depression. Psychotherapy appears to have a positive impact on the quality of life of patients with depression, beyond measurable reductions in depressive symptom severity. Mild depression treated with psychotherapy may be less likely to progress to severe depression. Psychoeducation alone can achieve remission for some patients.

• Therapists often use a combination of CBT and IPT or PST. IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends. IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy. Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. Time-limited psychodynamic therapy has also gained empirical support as a treatment for major depression.

Supportive interventions

• Self-help books are popular and bibliotherapy has demonstrated better efficacy than no treatment at all.

• Yoga may have a beneficial effect on depressive disorders, but there are significant variations in interventions, reporting, and feasibility.

• Other supportive interventions include relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture. In nonremitted patients, higher remission rates were observed in a higher-dose exercise group plus continuation of SSRI treatment compared with low-dose exercise plus SSRIs. Conversely, cessation of exercise may worsen depressive symptoms.

• St John’s wort is a herb that is considered to be effective for the treatment of mild to moderate depression. It may also be used as an alternative therapy (as...
monotherapy only) if there is no response to first- and second-line treatments.[164] [165] St John’s wort has an encouraging safety profile; however, numerous reports indicate the possibility of clinically significant drug-drug interactions, which must be taken into account before prescribing.[164] [165]

Computer-based treatment

• Evidence supports the efficacy of computer-based CBT,[141] [142] [143] [144] [145] [146] PST,[147] [148] and stress management.[149] However, high withdrawal rates are common.

Treatment-resistant/refractory depression

The majority of patients with depression do not respond adequately to their first antidepressant trial, but a substantial proportion of those will respond to a second antidepressant.[166] The general consensus is to consider a depressive illness that has not responded to two antidepressant trials of adequate dose and duration (preferably using two antidepressants with distinct mechanisms of action) to be treatment resistant or refractory.[167]

Although algorithms of the approach to treatment-refractory depression have been published, in practice algorithms are often altered or broken by variables unique to an individual patient. For example, side effects of medications, comorbid medical conditions, or affordability, along with psychosocial factors such as temperamental vulnerabilities, behavior patterns, and life circumstances, may all affect treatment. Clinical trials centred on individual patients may be feasible, but have not often been used.[168]

Reassessment

• Reassessment can be useful after an apparently failed course of treatment, as some of the residual symptoms of depression (e.g., social avoidance, sleep/wake reversal, a demoralized attitude) can reflect behavioral adaptations to depression, rather than the disease itself. In such cases, symptoms may best be corrected through behavioral intervention or psychotherapy rather than a new medication trial. With intermittent, brief follow-up visits it is also easy to miss mood-cycling that may occur between sessions that would indicate a bipolar spectrum disorder rather than pure major depression.

Antidepressant treatment

• Assuming major depressive disorder continues to be the most salient clinical problem, alternative options for treatment-resistant/refractory depression within the antidepressant class include monotherapy with a third (or fourth or fifth) SSRI, SNRI, or an atypical agent. Combined antidepressant therapy (i.e., an SSRI or SNRI plus bupropion or mirtazapine) may be indicated as a way of making optimal use of adverse effects (e.g., adding mirtazapine to an SNRI to facilitate sleep, or bupropion to an SSRI to try to improve sexual functioning); however, the evidence has not consistently supported a synergistic effect of combined antidepressants in alleviating depression.[169] [170] [171] [172] There is some evidence that failure on one or several antidepressants does not preclude later success.[173] [166] By the end of 4 different medication trials, 60% to 70% of patients are likely to respond to treatment. Although the general rule of thumb is to give antidepressants for at least 6 to 8 weeks, if there is no improvement at all in the first 2 weeks, switching may be appropriate at that point.[174]
When selecting a third (or fourth or fifth) medication to switch to, consider not only another SSRI, SNRI, or atypical agent (e.g., bupropion, mirtazapine), but also a tricyclic antidepressant (TCA) (e.g., amitriptyline, desipramine, doxepin, imipramine, or nortriptyline). Historically the first-line pharmacotherapy for depression, TCAs have fallen somewhat out of favor because of their adverse effects, the need for gradual dose increases, and their potential lethality in overdose. However, they remain effective and useful for many patients. Dose TCAs according to therapeutic blood monitoring. For most TCAs there is a minimum therapeutic level; for nortriptyline, uniquely, there is a therapeutic window delineating a range of effective levels.

In cases where nothing else has worked and the patient can tolerate a washout period from their current antidepressant, a monoamine oxidase inhibitor (MAOI) (e.g., isocarboxazid, phenelzine, selegiline, tranylcypromine) can be uniquely effective, even though it is associated with a more severe adverse effect profile and recommended only when other options prove ineffective. In cases where nothing else has worked and the patient can tolerate a washout period from their current antidepressant, a monoamine oxidase inhibitor (MAOI) (e.g., isocarboxazid, phenelzine, selegiline, tranylcypromine) can be uniquely effective, even though it is associated with a more severe adverse effect profile and recommended only when other options prove ineffective.[175] The washout period depends on the half-life of the antidepressant the patient is currently on and can range from 1 to 5 weeks. Do not use a MAOI without consulting a psychiatrist first.

Some studies show that combinations of antidepressants with other classes of medication are better than just a combination of different antidepressants alone.[176] In patients who have not responded to conventional antidepressants, lithium augmentation remains the best evidence-based approach; however, it is ideally initiated by a psychiatrist because of its narrow therapeutic index and risks of inadvertent toxicity from excessive dosing and drug-drug interactions. While these limitations make lithium unwieldy as a first-line treatment, evidence has emerged from one Finnish cohort study suggesting that lithium monotherapy is not only effective at preventing rehospitalization after severe depression, but is also more effective on its own than when combined with antidepressants.[177] The addition of an atypical antipsychotic to an antidepressant has been historically controversial[178] [179] however, augmentation with some agents is becoming more common practice and may improve outcomes.[180] [181] Second-generation antipsychotic medications used in combination with antidepressants demonstrate efficacy and their use is becoming widespread.[182] A commercially available olanzapine/fluoxetine combination has been shown to be superior to fluoxetine monotherapy and olanzapine monotherapy in producing early improvement in patients who have not responded to an antidepressant trial.[180] Aripiprazole, which the Food and Drug Administration (FDA) has approved for antidepressant augmentation, was found to be slightly more effective as augmentation than switching to a different antidepressant in US military veterans with treatment-resistant depression.[181] Brexiprazole, a novel serotonin-dopamine activity modulator, is approved by the FDA as an adjunctive treatment for major depressive disorder,[183] although the evidence for its efficacy derives from a relatively small number of studies.[184] Weight gain and akathisia are among the most commonly reported adverse effects, and small effects on glucose and lipids have also been noted.[185] While some benefit has been demonstrated in meta-analysis of clinical trial data, it is unclear whether benefits outweigh risks in people without psychosis.[178] Other augmentation strategies used by specialists include thyroid hormone, modafinil, ketamine, and pindolol.[186] [187] [188]

**Nonpharmacologic approaches**

- Check and ensure that the patient has started psychotherapy if multiple pharmacologic agents have been unsuccessful.
- When depression is severe enough to cause danger, significant distress, or functional impairment, the superior efficacy of ECT makes it a reliable and reasonable rescue treatment. The transient
impact on memory and cognition, which may reduce functioning during active treatment, make ECT less desirable for milder cases. It is important to remember that the effects of ECT generally last only a few weeks, so pharmacotherapy is necessary to sustain its effects or act as maintenance therapy.

**Recurrent episodes**

Recurrent episodes of major depression should be treated with the same antidepressant that previously induced remission, provided that the recurrences do not occur while under adequate maintenance treatment with such medication. Consider maintenance therapy for at least 3 to 5 years or lifetime for patients who have had their third episode of depression.[103] Patients with a first recurrence and risk factors for further recurrences (including family history of bipolar disorder, recurrence within 1 year, onset in adolescence, severe depression or suicide attempt, and sudden onset of symptoms) may also benefit from long-term maintenance therapy. The selection and success of these treatments depends on the type and severity of depressive symptoms, but most often relies on trial and error. Psychotherapy in patients who suffer from recurrent episodes may be well aimed if it addresses the despair patients often feel when they see recovery as only a temporary respite from suffering, and if it educates patients about ways to cope with and possibly prevent recurrences.

**Pregnancy**

Depression coinciding with pregnancy creates a significant clinical dilemma. On the one hand, the fetus is exposed to a potential for harm by the increased likelihood of maternal substance misuse, neglect of health, or suicide. On the other hand, all antidepressants cross the placental barrier, with the potential to cause iatrogenic harm to the fetus. Fortunately, studies of the safety of antidepressant use in pregnancy for the most part add up to minimal, if any, risk to the fetus.[189] [190] Unfortunately, there is little controlled trial evidence.[191] Consistent data to support fully-informed decision-making are lacking.[192] [193] [194] [195] [196] [197] [198]

Antidepressant risks can extend to and beyond birth. The results of one systematic review and meta-analysis found that maternal SSRI use (but not depression without SSRI use) is associated with an increased risk of preterm birth.[199] Another systematic review and meta-analysis found that pregnant women with untreated depression have an increased risk of preterm birth and low birth weight compared with women without depression, suggesting that untreated depression itself may be a risk factor for early delivery.[200] Transient irritability and other symptoms reminiscent of antidepressant discontinuation syndromes affect a substantial proportion of neonates exposed to antidepressants in utero up to the time of delivery.[201]

Evidence of a relationship between depression, antidepressant treatment, and autism spectrum disorders (ASD) is mixed, with some studies showing an association between maternal antidepressant use during pregnancy and a slightly increased risk of ASD in the child; other studies show increased risk of ASD in children of mothers with a prenatal psychiatric disorder and no antidepressant use.[202] [203] [204]

It is fairly clear that women who stop their antidepressant are more likely to have a relapse of depression during their pregnancy.[205] Depression itself may negatively affect fetal development (e.g., causing hyperactivity and irregular fetal heart rate), increase infants’ cortisol levels, impact on infant temperament, and influence behavior in later childhood and adolescence.[206]

The best recommendation that might arise from all of these weak and/or contradictory data is for clinicians to carefully discuss the risks of remaining on antidepressant treatment during pregnancy,
Depression in adults

Treatment

against the risks of stopping or avoiding antidepressants and exposing the fetus to the harmful effects of prepartum depression. Despite the lack of consistent evidence of harmful effects of antidepressants to fetal and infant health and development, caution is required. Updated information about potential harms from antidepressants and other pharmaceuticals can be found at various resources. [MotherToBaby]

For women with severe major depression in pregnancy, ECT may be the treatment of choice as it does not expose the fetus to any known risk.[207] [208] For moderate to severe episodes, there is little consistent controlled trial evidence that antidepressants should be contraindicated during pregnancy; the risk to the fetus from the potentially harmful effects of the mother’s untreated depression on her health apparently outweighs any detectable risk to the fetus from antidepressants.[209] [190] [191] Treat mild depression in pregnancy as you would any other, perhaps with a slightly higher threshold for using medication than you would with a nonpregnant patient. The risk/benefit balance may tip in favor of nonpharmacologic therapies, particularly because many patients may have reservations about using medication when pregnant. CBT is associated with a moderate treatment effect for major depressive disorder during pregnancy. Interpersonal psychotherapy also appears to have a treatment effect, but to a lesser extent than CBT.[210]

There is evidence to support the use of counseling interventions, such as CBT and interpersonal psychotherapy, to prevent depression in pregnant and postpartum women who are at relatively high risk for depression due to family history, stressful life circumstances, and medical complications of pregnancy and delivery to mother and baby.[60]

Postpartum depression

Screen women with risk factors for postpartum depression to prevent or immediately treat postpartum depression. There is evidence from combined studies that CBT may be effective for both prevention and treatment of postpartum depressive symptoms.[211] Longer-term therapy may further enhance psychotherapeutic benefits to mothers and their offspring. Pharmacotherapy requires careful consideration. Many breast-feeding women choose not to take medication because of concerns about infant exposure. Clinicians should have a higher threshold for prescribing psychotropic medications during pregnancy and breast-feeding. Fetal and newborn exposure, however small a risk statistically, nonetheless changes the fundamental risk-benefit equation because of the potential for long-term impact on the fetus or newborn. With increasing severity of depression, the equation might tip towards pharmacotherapy. In women who have had severe episodes of major depression, the slight risk to the fetus or baby must be weighed against the risk posed by depression in the mother, of self- or infant-neglect, or suicidal behavior.

Updated information about potential harms to breast-feeding infants from antidepressants and other pharmaceuticals can be found at various resources. [TOXNET: LactMed]

For more detailed information, please see our separate topic on Postpartum depression.

Perimenopausal women

Although symptoms of oncoming menopause can complicate the experience of depression in women, risk for depression in this population is more closely associated with prior depression than with hormonal status, and treatment is the same as for other patients.[212]
Seasonal affective disorder

Seasonal affective disorder (SAD) is a subtype of major depression, occurring with seasonal change. SAD occurs more commonly in northern latitudes and responds to bright-light or blue-light therapy, preferably combined with CBT,[213] as well as adjuvant therapy with antidepressants.

For more detailed information, please see our separate topic on Seasonal affective disorder.

Comorbidities

Antidepressants may be effective in reducing depression and alcohol consumption in patients with comorbid depression and alcohol dependence.[214] Antidepressant use in depressed patients who are on opioid agonist therapy is not well supported.[215] Available evidence on the use of antidepressants with depression comorbid with dementia is poor, suggesting their potential value may be outweighed in many cases by the potential for adverse effects.[216] Evidence is also low quality, but more favorable, for antidepressants in patients with depression and HIV infection.[217] Support for antidepressants for depression comorbid with cancer is mixed.[218] [219]

Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer
### Acute

<table>
<thead>
<tr>
<th>Depression Type</th>
<th>1st Treatment</th>
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<tbody>
<tr>
<td>Severe depression, nonpregnant: psychotic, suicidal, severe psychomotor retardation impeding activities of daily living, catatonia, or severe agitation</td>
<td>psychiatric referral ± hospitalization + antidepressant</td>
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<td></td>
<td>adjunct immediate symptom management with benzodiazepine ± antipsychotic</td>
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<td></td>
<td>1st psychiatric referral ± hospitalization + electroconvulsive therapy (ECT)</td>
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<td>plus antidepressant</td>
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<td>adjunct immediate symptom management with benzodiazepine ± antipsychotic</td>
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#### Moderate Depression, Nonpregnant

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<tbody>
<tr>
<td>Moderate depression, nonpregnant: severe symptoms, significant impairment but no psychotic symptoms, no suicidal ideation, and no severe psychomotor retardation or agitation</td>
<td>antidepressant</td>
</tr>
<tr>
<td></td>
<td>adjunct psychotherapy or other nonpharmacologic treatment</td>
</tr>
<tr>
<td></td>
<td>adjunct immediate symptom management with benzodiazepine ± antipsychotic</td>
</tr>
<tr>
<td></td>
<td>2nd switch to alternative antidepressant</td>
</tr>
</tbody>
</table>

#### Mild Depression, Nonpregnant

<table>
<thead>
<tr>
<th>Depression Type</th>
<th>1st Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild depression, nonpregnant: low to moderate severity symptoms, partial impairment, no psychotic symptoms, no suicidal ideation, and no psychomotor retardation or agitation</td>
<td>antidepressant</td>
</tr>
<tr>
<td></td>
<td>1st psychotherapy</td>
</tr>
<tr>
<td></td>
<td>1st supportive interventions</td>
</tr>
<tr>
<td></td>
<td>1st computer-based interventions</td>
</tr>
<tr>
<td></td>
<td>2nd switch to alternative antidepressant#</td>
</tr>
<tr>
<td></td>
<td>3rd St John’s wort</td>
</tr>
</tbody>
</table>
## Treatment

### Acute

<table>
<thead>
<tr>
<th>treatment-resistant/refractory depression</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>reassess and switch to alternative antidepressant or try combination therapy plus consider augmentation therapy plus psychotherapy or other nonpharmacologic treatment</td>
</tr>
<tr>
<td>2nd</td>
<td>monoamine oxidase inhibitor (MAOI) plus psychotherapy or other nonpharmacologic treatment</td>
</tr>
<tr>
<td>3rd</td>
<td>electroconvulsive therapy (ECT)</td>
</tr>
</tbody>
</table>

### Pregnant

<table>
<thead>
<tr>
<th></th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>antidepressant or electroconvulsive therapy (ECT) plus psychotherapy</td>
</tr>
</tbody>
</table>

### Ongoing

<table>
<thead>
<tr>
<th>treatment responsive</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>maintenance antidepressant therapy adjunct psychotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>recurrent episode</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>repeat of remission-inducing regimen or long-term therapy plus psychotherapy</td>
</tr>
</tbody>
</table>
Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Acute

**severe depression, nonpregnant:** psychotic, suicidal, severe psychomotor retardation impeding activities of daily living, catatonia, or severe agitation

<table>
<thead>
<tr>
<th>1st psychiatric referral ± hospitalization + antidepressant</th>
</tr>
</thead>
</table>

#### Primary options

- **citalopram:** 20 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day

  OR

- **escitalopram:** 10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

  OR

- **fluoxetine:** 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 80 mg/day; doses >20 mg/day may be given in 2 divided doses

  A delayed-release, once-weekly formulation is available for maintenance therapy.

  OR

- **paroxetine:** 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 50 mg/day; 25 mg orally (controlled-release) once daily initially, increase gradually according to response, maximum 62.5 mg/day

  OR

- **sertraline:** 50 mg orally once daily initially, increase gradually according to response, maximum 200 mg/day

  OR

- **desvenlafaxine:** 50 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day; doses >50 mg/day have not shown additional benefit

  OR
### Acute

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>duloxetine</td>
<td>40-60 mg/day orally initially given in 1-2 divided doses, increase gradually according to response, maximum 120 mg/day; doses &gt;60 mg/day have not shown additional benefit</td>
</tr>
<tr>
<td>levomilnacipran</td>
<td>20 mg orally once daily initially for 2 days, increase to 40 mg once daily, then increase gradually according to response, maximum 120 mg/day</td>
</tr>
<tr>
<td>venlafaxine</td>
<td>75 mg/day orally (immediate-release) initially given in 2-3 divided doses, increase gradually according to response, maximum 225 mg/day; 75 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 225 mg/day</td>
</tr>
<tr>
<td>bupropion hydrochloride</td>
<td>100 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 450 mg/day given in 2-3 divided doses; 150 mg orally (sustained-release) once daily initially, increase gradually according to response, maximum 400 mg/day given in 2 divided doses; 150 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 450 mg/day</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>15 mg orally once daily initially, increase gradually according to response, maximum 45 mg/day</td>
</tr>
<tr>
<td>vilazodone</td>
<td>10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
</tr>
<tr>
<td>vortioxetine</td>
<td>5-10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day</td>
</tr>
</tbody>
</table>
Depression in adults

**Treatment**

<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>» The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.</td>
</tr>
<tr>
<td>» Refer patient to a psychiatrist. Suicide risk assessment is critical. Consider hospitalisation if patients: have significant suicidal ideation or intent and lack adequate safeguards in their family environment; have intent to hurt others; are unable to care for themselves and adhere to their treatment; have psychotic symptoms, or have uncontrolled agitation accompanied by the risk of impulsive behavior. If the patient is unwilling to be hospitalized, engage family support and, if necessary, exercise legal means to compel treatment.</td>
</tr>
<tr>
<td>» Agitated patients require high levels of care because of their enhanced emotional distress and the risk of impulsive violence. Severe impairment of the activities of daily living due to catatonia or psychomotor retardation increases the severity of depression, as patients who are inert and bedbound, or not taking adequate sustenance, run the risk of a deterioration in health while awaiting a response to pharmacotherapy. These patients may require supportive nursing care.</td>
</tr>
<tr>
<td>» Antidepressant therapy is usually the first line option in most patients. Electroconvulsive therapy (ECT) is the first-line treatment in some severe cases, but when immediate ECT is either not indicated or not an option, antidepressant pharmacotherapy is crucial.</td>
</tr>
<tr>
<td>» Commonly used antidepressants include selective serotonin-reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone, vortioxetine).</td>
</tr>
<tr>
<td>» No consistent differences in safety or efficacy have been demonstrated between antidepressants,[84] although some head-to-head efficacy and acceptability differences have been revealed in one large meta-analysis, and might be considered among many factors in treatment selection.[82] According to one different meta-analysis of individual patient data from 15 controlled trials of acute-phase treatment of major depression, mirtazapine may be more rapidly effective than SSRIs.[85]</td>
</tr>
</tbody>
</table>
### Acute

- Choice of drug should be based on patient preference, tolerability, and past evidence of effectiveness in the patient. Some clinicians may also have a lower threshold for considering treatment with an antidepressant that has been shown to be effective in a family member. One rationale for this is that a person who has seen a family member respond to a particular drug may find treatment with this drug more acceptable and may have increased expectations for recovery. This, however, is not an evidence-based approach; advances in pharmacogenomics (examining the impact of heritable genetic factors on treatment efficacy and tolerability for individual patients) may eventually provide clarification, but pharmacogenomic analysis is not yet recommended for widespread use.[86]

- Although the net result of antidepressant response is a significant reduction in suicidal ideation,[80] [87] there is some evidence of increased suicidal behavior in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[88] [89] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.[90] [91] The results of one large meta-analysis suggest that, in adults under the age of 25 years, the risk of both emergence and worsening of suicidality may be raised in weeks 3-6 of treatment (but not in weeks 1-2), which is later than has been suggested by other studies.[92]

- Determine antidepressant dose based on known target dose range. High-dose SSRI treatment for depression in patients refractory to medium-dose treatment is not recommended.[220] In a minority of patients, pharmacogenomic testing may indicate using a low-end or high-end dose depending on genotype. On balance, there is no evidence to support routinely increasing the dose beyond the established dose range.[93]

- Follow up patients 1-2 weeks after initiating therapy, then monthly for the next 12 weeks. If systematic evaluation is preferred, use the Patient Health Questionnaire-9 (PHQ-9) to assess changes in symptom severity. Titrate the antidepressant dose to the maximum tolerated in patients who experience a partial response after 2-4 weeks. Patients are likely to begin to show a response within the first 1-2 weeks of treatment; however, successful antidepressant therapy to
### Acute

The point of remission of all symptoms may take 6-8 weeks. A 50% decrease in symptom score constitutes an adequate response, and a 25% to 50% change in symptom score may indicate the need to modify treatment.

- Continue successful antidepressant treatment for 9-12 months following remission;\[102\] \[103\] 2[A] Evidence however, some physicians recommend that patients with frequent recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.

**adjunct**

**Immediate symptom management with benzodiazepine ± antipsychotic**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- lorazepam: consult specialist for guidance on dose

OR

- clonazepam: consult specialist for guidance on dose

OR

- risperidone: consult specialist for guidance on dose

OR

- olanzapine: consult specialist for guidance on dose

OR

- quetiapine: consult specialist for guidance on dose

OR

- fluphenazine: consult specialist for guidance on dose

OR

- trazodone: consult specialist for guidance on dose

The specific drug regimens above are examples of commonly used regimens only.
Depression in adults

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consult local guidance for other examples and preferred options.</td>
</tr>
</tbody>
</table>

» Emergency treatment of mood disorder symptoms aims to stabilize a situation that otherwise leaves the patient in danger from suicidal impulses or extreme self-neglect, and leaves third parties in danger due to unpredictable, impulsive, or aggressive behavior. Treatment with a benzodiazepine and/or antipsychotic may also bring immediate relief from insomnia, anxiety, agitation, and persistent ruminative thinking while waiting the expected several weeks for significant symptom remission from the antidepressant.

» Because antipsychotics tend to have significant clinical effects more rapidly than antidepressants, the decision to employ one is more urgent than to use an antidepressant. Have a lower threshold for adding an antipsychotic to antidepressant treatment in severe cases under several circumstances. Antidepressants alone may not effectively address psychotic symptoms, such as delusions or hallucinations.[74]

» Patients with catatonia can be treated with a benzodiazepine (e.g., lorazepam, clonazepam). Patients with psychosis or severe agitation can be treated with an antipsychotic (e.g., risperidone, olanzapine, quetiapine, fluphenazine). Patients with mild agitation or severe anxiety can be treated with a benzodiazepine and/or an antipsychotic. Patients with insomnia can be treated with quetiapine or trazodone. Antipsychotics are more appropriate where there is risk of benzodiazepine dependence.

» Dose to effectiveness: if the benzodiazepine or antipsychotic fails to produce an effect and is tolerated, increase the dose with caution up to the recommended maximum. If it fails at the maximum dose or leads to intolerable adverse effects at lower doses, switch to another agent.

» Patients should not drive while taking these tranquilizing agents.

1st psychiatric referral ± hospitalization + electroconvulsive therapy (ECT)

» Refer patient to a psychiatrist. Suicide risk assessment is critical. Consider hospitalization if patients: have significant suicidal ideation or intent and lack adequate safeguards in their family environment; have intent to hurt others; are unable to care for themselves and adhere...
Depression in adults

Treatment

Acute

- to their treatment; have psychotic symptoms, or have uncontrolled agitation accompanied by the risk of impulsive behavior. If the patient is unwilling to be hospitalized, engage family support and, if necessary, exercise legal means to compel treatment.

  » Agitated patients require high levels of care because of their enhanced emotional distress and the risk of impulsive violence. Severe impairment of the activities of daily living due to catatonia or psychomotor retardation increases the severity of depression, as patients who are inert and bedbound, or not taking adequate sustenance, run the risk of a deterioration in health while awaiting a response to pharmacotherapy. These patients may require supportive nursing care.

  » In certain patients with severe depression who have psychotic features, have active suicidal thoughts, or are unresponsive to or intolerant of antidepressants, ECT may be considered first-line treatment.[221] It may be used early in treatment for psychosis, suicidality, or catatonia. ECT is often the treatment of choice for severely depressed older patients; it is effective,[75] and avoids the complications that may arise from pharmacologic intolerance and drug interactions associated with treatment for comorbid physical conditions.

  » ECT is performed under general anesthesia, 2 or 3 times a week for a total of 6-12 treatments.

  » Patient and clinician must be fully informed of the potential risks, so that the patient can provide informed consent. The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments,[76] [77] meaning that it is one of the safer procedures performed under general anesthetic. The risk of death may be increased in patients with coronary heart disease, due to a theoretical increased risk of ischemia during the induced seizure. According to one systematic review, the majority of patients report adverse cognitive effects during and shortly after treatment, most commonly memory loss (both anterograde and retrograde amnesia).[78] This impairment seems to be short-lived according to objective assessment,[79] although a significant proportion of patients report persistent memory loss following ECT.[78] This potential risk must be balanced against the evidence in favor of its efficacy, especially in patients with severe depression.

  plus antidepressant
<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
</tbody>
</table>

**Primary options**

- **citalopram**: 20 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day

OR

- **escitalopram**: 10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

OR

- **fluoxetine**: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 80 mg/day; doses >20 mg/day may be given in 2 divided doses
  A delayed-release, once-weekly formulation is available for maintenance therapy.

OR

- **paroxetine**: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 50 mg/day; 25 mg orally (controlled-release) once daily initially, increase gradually according to response, maximum 62.5 mg/day

OR

- **sertraline**: 50 mg orally once daily initially, increase gradually according to response, maximum 200 mg/day

OR

- **desvenlafaxine**: 50 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day; doses >50 mg/day have not shown additional benefit

OR

- **duloxetine**: 40-60 mg/day orally initially given in 1-2 divided doses, increase gradually according to response, maximum 120 mg/day; doses >60 mg/day have not shown additional benefit
Depression in adults

Treatment

Acute

- **levomilnacipran**: 20 mg orally once daily initially for 2 days, increase to 40 mg once daily, then increase gradually according to response, maximum 120 mg/day

OR

- **venlafaxine**: 75 mg/day orally (immediate-release) initially given in 2-3 divided doses, increase gradually according to response, maximum 225 mg/day; 75 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 225 mg/day

OR

- **bupropion hydrochloride**: 100 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 450 mg/day given in 2-3 divided doses; 150 mg orally (sustained-release) once daily initially, increase gradually according to response, maximum 400 mg/day given in 2 divided doses; 150 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 450 mg/day

OR

- **mirtazapine**: 15 mg orally once daily initially, increase gradually according to response, maximum 45 mg/day

OR

- **vilazodone**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day

OR

- **vortioxetine**: 5-10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

> The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.

> Commonly used antidepressants include selective serotonin-reuptake inhibitors.
Depression in adults

Treatment

Acute

(SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone, vortioxetine).

» No consistent differences in safety or efficacy have been demonstrated between antidepressants,[84] although some head-to-head efficacy and acceptability differences have been revealed in one large meta-analysis, and might be considered among many factors in treatment selection.[82] According to one different meta-analysis of individual patient data from 15 controlled trials of acute-phase treatment of major depression, mirtazapine may be more rapidly effective than SSRIs.[85]

» Choice of drug should be based on patient preference, tolerability, and past evidence of effectiveness in the patient. Some clinicians may also have a lower threshold for considering treatment with an antidepressant that has been shown to be effective in a family member. One rationale for this is that a person who has seen a family member respond to a particular drug may find treatment with this drug more acceptable and may have increased expectations for recovery. This, however, is not an evidence-based approach; advances in pharmacogenomics (examining the impact of heritable genetic factors on treatment efficacy and tolerability for individual patients) may eventually provide clarification, but pharmacogenomic analysis is not yet recommended for widespread use.[86]

» Although the net result of antidepressant response is a significant reduction in suicidal ideation,[80] [87] there is some evidence of increased suicidal behavior in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[88] [89] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.[90] [91] The results of one large meta-analysis suggest that, in adults under the age of 25 years, the risk of both emergence and worsened suicidality may be raised in weeks 3-6 of treatment (but not in weeks 1-2), which is later than has been suggested by other studies.[92]

» Determine antidepressant dose based on known target dose range. High-dose
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SSRI treatment for depression in patients refractory to medium-dose treatment is not recommended.[220] In a minority of patients, pharmacogenomic testing may indicate using a low-end or high-end dose depending on genotype. On balance, there is no evidence to support routinely increasing the dose beyond the established dose range.[93]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up patients 1-2 weeks after initiating therapy, then monthly for the next 12 weeks. If you prefer systematic evaluation, use the Patient Health Questionnaire-9 (PHQ-9) to assess changes in symptom severity. Titrate the antidepressant dose to the maximum tolerated in patients who experience a partial response after 2-4 weeks. Patients are likely to begin to show a response within the first 1-2 weeks of treatment; however, successful antidepressant therapy to the point of remission of all symptoms may take 6-8 weeks. A 50% decrease in symptom score constitutes an adequate response, and a 25% to 50% change in symptom score may indicate the need to modify treatment.</td>
<td></td>
</tr>
<tr>
<td>Continue successful antidepressant treatment for 9-12 months following remission;[102] [103] Evidence however, some physicians recommend that patients with frequent recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.</td>
<td></td>
</tr>
</tbody>
</table>

#### adjunct immediate symptom management with benzodiazepine ± antipsychotic

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **lorazepam**: consult specialist for guidance on dose

  OR

- **clonazepam**: consult specialist for guidance on dose

  OR

- **risperidone**: consult specialist for guidance on dose

  OR

- **olanzapine**: consult specialist for guidance on dose
Depression in adults

**Treatment**

<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» quetiapine: consult specialist for guidance on dose</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» fluphenazine: consult specialist for guidance on dose</td>
</tr>
<tr>
<td>OR</td>
</tr>
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<td>» trazodone: consult specialist for guidance on dose</td>
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<tr>
<td>» The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.</td>
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<tr>
<td>» Emergency treatment of mood disorder symptoms aims to stabilize a situation that otherwise leaves the patient in danger from suicidal impulses or extreme self-neglect, and leaves third parties in danger due to unpredictable, impulsive, or aggressive behavior. Treatment with a benzodiazepine and/or antipsychotic may also bring immediate relief from insomnia, anxiety, agitation, and persistent ruminative thinking while waiting the expected several weeks for significant symptom remission from the electroconvulsive therapy.</td>
</tr>
<tr>
<td>» Patients with catatonia can be treated with a benzodiazepine (e.g., lorazepam, clonazepam). Patients with psychosis or severe agitation can be treated with an antipsychotic (e.g., risperidone, olanzapine, quetiapine, fluphenazine). Patients with mild agitation or severe anxiety can be treated with a benzodiazepine and/or an antipsychotic. Patients with insomnia can be treated with quetiapine or trazodone. Antipsychotics are more appropriate where there is risk of benzodiazepine dependence.</td>
</tr>
<tr>
<td>» Dose to effectiveness: if the benzodiazepine or antipsychotic fails to produce an effect and is tolerated, increase the dose with caution up to the recommended maximum. If it fails at the maximum dose or leads to intolerable adverse effects at lower doses, switch to another agent.</td>
</tr>
<tr>
<td>» Patients should not drive while taking these tranquilizing agents.</td>
</tr>
</tbody>
</table>

2nd switch to alternative antidepressant
Depression in adults

TREATMENT

Acute

» If the response to first-line therapy is inadequate, consider switching to an alternative antidepressant.\[94\] [95] By the end of four different medication trials, 60% to 70% of patients are likely to respond to treatment. Switching may be appropriate if no improvement in symptoms has occurred within the first 2 weeks of treatment;[96] [97] however, early response may be, but is not necessarily, a reliable indicator of continued response.[98] [99] Continue treatment if there has been some improvement for at least the full 6-8 weeks, but do not continue prescribing a drug providing inadequate benefit indefinitely. Of note, in patients with no initial improvement to treatment with fluoxetine, one study showed the likelihood of converting to a positive response decreased the longer patients remained unimproved.[100]

» Consider a change in drug class; if a patient was on a selective serotonin-reuptake inhibitor, then try a serotonin norepinephrine-reuptake inhibitor. If treatment was not tolerated due to adverse effects, retry with an agent with fewer or different adverse effects. If an agent is switched, resume weekly follow-up until a response is apparent.

» Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. The timeframe required for safely switching depends on various factors, including the pharmacokinetic properties of the drugs and possible interactions between them, as well as patient characteristics such as age, sensitivity to adverse effects, and the capacity to wait to begin a new course of treatment. In some situations, it is possible to give both drugs for a short period of time while the changeover is occurring; however, this should only be done under specialist guidance. In other cases, it is safer to take a more conservative approach. This involves slowly tapering the dose of the first drug before stopping it, and then waiting a period of time before starting the second drug (known as a washout period, which is usually five half-lives of the first drug). Drugs with longer half-lives (e.g., fluoxetine) require longer washout periods (e.g., up to 5-6 weeks) when combined with a drug with which the combination is contraindicated (e.g., monoamine oxidase inhibitors with fluoxetine). Specific recommendations for switching from one antidepressant to another, along with suitable washout periods, are available and local guidance should be consulted. When in doubt,
# Treatment

**Acute**

In the absence of such guidelines, as a general principle perform a drug interaction check to be sure there are no absolute contraindications, and then “start low and go slow” until safety can be ascertained.

- Continue successful antidepressant treatment for 9-12 months following remission;[102] [103] [Evidence] however, some physicians recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.

- If there is an inadequate response to two (or more) full-dose and duration antidepressants, the patient’s depression might be considered treatment resistant or refractory, and warrants a more complex approach.

<table>
<thead>
<tr>
<th>moderate depression, nonpregnant: severe symptoms, significant impairment but no psychotic symptoms, no suicidal ideation, and no severe psychomotor retardation or agitation</th>
<th>1st antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>- <strong>citalopram</strong>: 20 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- <strong>escitalopram</strong>: 10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- <strong>fluoxetine</strong>: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 80 mg/day; doses &gt;20 mg/day may be given in 2 divided doses. A delayed-release, once-weekly formulation is available for maintenance therapy.</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>- <strong>paroxetine</strong>: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 50 mg/day; 25 mg orally (controlled-release) once...</td>
<td></td>
</tr>
</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>daily initially, increase gradually according to response, maximum 62.5 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» sertraline: 50 mg orally once daily initially, increase gradually according to response, maximum 200 mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» desvenlafaxine: 50 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day; doses &gt;50 mg/day have not shown additional benefit</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» duloxetine: 40-60 mg/day orally initially given in 1-2 divided doses, increase gradually according to response, maximum 120 mg/day; doses &gt;60 mg/day have not shown additional benefit</td>
<td></td>
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<tr>
<td>OR</td>
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<tr>
<td>» levomilnacipran: 20 mg orally once daily initially for 2 days, increase to 40 mg once daily, then increase gradually according to response, maximum 120 mg/day</td>
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<tr>
<td>OR</td>
<td></td>
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<tr>
<td>» venlafaxine: 75 mg/day orally (immediate-release) initially given in 2-3 divided doses, increase gradually according to response, maximum 225 mg/day; 75 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 225 mg/day</td>
<td></td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» bupropion hydrochloride: 100 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 450 mg/day given in 2-3 divided doses; 150 mg orally (sustained-release) once daily initially, increase gradually according to response, maximum 400 mg/day given in 2 divided doses; 150 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 450 mg/day</td>
<td></td>
</tr>
</tbody>
</table>
**Acute**

OR

» **mirtazapine**: 15 mg orally once daily initially, increase gradually according to response, maximum 45 mg/day

OR

» **vilazodone**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day

OR

» **vortioxetine**: 5-10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.

Commonly used antidepressants include selective serotonin-reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone, vortioxetine).

No consistent differences in safety or efficacy have been demonstrated between antidepressants,[84] although some head-to-head efficacy and acceptability differences have been revealed in one large meta-analysis, and might be considered among many factors in treatment selection.[82] According to one different meta-analysis of individual patient data from 15 controlled trials of acute-phase treatment of major depression, mirtazapine may be more rapidly effective than SSRIs.[85]

Choice of drug should be based on patient preference, tolerability, and past evidence of effectiveness in the patient. Some clinicians may also have a lower threshold for considering treatment with an antidepressant that has been shown to be effective in a family member. One rationale for this is that a person who has seen a family member respond to a particular drug may find treatment with this drug more acceptable and may have increased expectations for recovery. This,
however, is not an evidence-based approach; advances in pharmacogenomics (examining the impact of heritable genetic factors on treatment efficacy and tolerability for individual patients) may eventually provide clarification, but pharmacogenomic analysis is not yet recommended for widespread use.\[86\]

» Although the net result of antidepressant response is a significant reduction in suicidal ideation,\[80\] \[87\] there is some evidence of increased suicidal behavior in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.\[88\] \[89\] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.\[90\] \[91\] The results of one large meta-analysis suggest that in adults under the age of 25, the risk of both emergence and worsening of suicidality may be raised in weeks 3-6 of treatment (but not in weeks 1-2), which is later than has been suggested by other studies.\[92\]

» Determine antidepressant dose based on known target dose range. High-dose SSRI treatment for depression in patients refractory to medium-dose treatment is not recommended.\[220\] In a minority of patients, pharmacogenomic testing may indicate using a low-end or high-end dose depending on genotype. On balance, there is no evidence to support routinely increasing the dose beyond the established dose range.\[93\]

» Follow up patients 1-2 weeks after initiating therapy, then monthly for the next 12 weeks. If you prefer systematic evaluation, use the Patient Health Questionnaire-9 (PHQ-9) to assess changes in symptom severity. Titrate the antidepressant dose to the maximum tolerated in patients who experience a partial response after 2-4 weeks. Patients are likely to begin to show a response within the first 1-2 weeks of treatment; however, successful antidepressant therapy to the point of remission of all symptoms may take 6-8 weeks. A 50% decrease in symptom score constitutes an adequate response, and a 25% to 50% change in symptom score may indicate the need to modify treatment.

» Continue successful antidepressant treatment for 9-12 months following remission;\[102\] \[103\] 2[A]Evidence however, some physicians recommend that patients with frequent recurrences and relapses, who respond...
Acute

Adjunct psychotherapy or other nonpharmacologic treatment

Treatment recommended for SOME patients in selected patient group

» Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[105] [106]

» In addition to pharmacotherapeutic strategies, cognitive behavioral therapy (CBT) has shown greater efficacy than pharmacologic placebo across levels of severity.[107] Treatment response to CBT is comparable with antidepressant response in some studies.[108] Staged treatment trials suggest that CBT may be particularly beneficial when used during the continuation phase of treatment; CBT reduces the risk of relapse/recurrence at least as well as, and perhaps better than, antidepressant continuation.[109] [110] [111] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[112] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[113]

» Therapists often use a combination of CBT Evidence and interpersonal psychotherapy (IPT) Evidence or problem-solving therapy (PST).[114] [115] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[117] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[118] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. PST focuses on training in adaptive problem-solving attitudes and skills.[115] [119]

» Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[120]

» Behavioral activation is a less cerebral, more behavioral alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomized controlled trial found it to be no less effective than CBT for adults with depression.[121]
### Treatment

#### Acute

<table>
<thead>
<tr>
<th>adjunct</th>
<th>immediate symptom management with benzodiazepine ± antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td>» lorazepam: consult specialist for guidance on dose</td>
</tr>
<tr>
<td>OR</td>
<td>» clonazepam: consult specialist for guidance on dose</td>
</tr>
<tr>
<td>OR</td>
<td>» quetiapine: consult specialist for guidance on dose</td>
</tr>
<tr>
<td>OR</td>
<td>» trazodone: consult specialist for guidance on dose</td>
</tr>
<tr>
<td></td>
<td>The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.</td>
</tr>
<tr>
<td></td>
<td>» Patients with mild agitation or severe anxiety can be treated with a benzodiazepine (e.g., lorazepam, clonazepam) and/or an antipsychotic (e.g., quetiapine). Patients with insomnia can be treated with quetiapine or trazodone. Antipsychotics are more appropriate where there is risk of benzodiazepine dependence.</td>
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<tr>
<td></td>
<td>» Dose to effectiveness: if the benzodiazepine or antipsychotic fails to produce an effect and is tolerated, increase the dose with caution up to the recommended maximum. If it fails at the maximum dose or leads to intolerable adverse effects at lower doses, switch to another agent.</td>
</tr>
<tr>
<td></td>
<td>» Patients should not drive while taking these tranquilizing agents.</td>
</tr>
</tbody>
</table>

#### 2nd switch to alternative antidepressant

|         | If the response to first-line therapy is inadequate, consider switching to an alternative antidepressant.[94] [95] By the end of four different medication trials, 60% to 70% of patients are likely to respond to treatment. Switching may be appropriate if no improvement in symptoms has occurred within the first 2
Depression in adults

**Acute**

weeks of treatment;[96] [97] however, early response may be, but is not necessarily, a reliable indicator of continued response.[98] [99] Continue treatment if there has been some improvement for at least the full 6-8 weeks, but do not continue prescribing a drug providing inadequate benefit indefinitely. Of note, in patients with no initial improvement to treatment with fluoxetine, one study showed the likelihood of converting to a positive response decreased the longer patients remained unimproved.[100]

» Consider a change in drug class; if a patient was on a selective serotonin-reuptake inhibitor, then try a serotonin norepinephrine-reuptake inhibitor. If treatment was not tolerated due to adverse effects, retry with an agent with fewer or different adverse effects.

» Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. The timeframe required for safely switching depends on various factors, including the pharmacokinetic properties of the drugs and possible interactions between them, as well as patient characteristics such as age, sensitivity to adverse effects, and the capacity to wait to begin a new course of treatment. In some situations, it is possible to give both drugs for a short period of time while the changeover is occurring; however, this should only be done under specialist guidance. In other cases, it is safer to take a more conservative approach. This involves slowly tapering the dose of the first drug before stopping it, and then waiting a period of time before starting the second drug (known as a washout period, which is usually five half-lives of the first drug). Drugs with longer half-lives (e.g., fluoxetine) require longer washout periods (e.g., up to 5-6 weeks) when combined with a drug with which the combination is contraindicated (e.g., monoamine oxidase inhibitors with fluoxetine). Specific recommendations for switching from one antidepressant to another, along with suitable washout periods, are available and local guidance should be consulted. When in doubt, in the absence of such guidelines, as a general principle perform a drug interaction check to be sure there are no absolute contraindications, and then “start low and go slow” until safety can be ascertained.

» Continue successful antidepressant treatment for 9-12 months following remission;[102] [103] [2[A]Evidence however, some physicians
## Treatment

### Acute

recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.

» If there is an inadequate response to two (or more) full-dose and duration antidepressants, the patient’s depression might be considered treatment resistant or refractory, and warrants a more complex approach.

adjunct psychotherapy or other nonpharmacologic treatment

<table>
<thead>
<tr>
<th>Treatment recommended for SOME patients in selected patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td>» Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[105] [106]</td>
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<tr>
<td>» In addition to pharmacotherapeutic strategies, cognitive behavioral therapy (CBT) has shown greater efficacy than pharmacologic placebo across levels of severity.[107]</td>
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<tr>
<td>» Therapists often use a combination of CBT[3][Evidence and interpersonal psychotherapy (IPT)[114] [4][Evidence or problem-solving therapy (PST).[115] [116] ] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[117]</td>
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<tr>
<td>» Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[120]</td>
</tr>
</tbody>
</table>
### Acute

Behavioral activation is a less cerebral, more behavioral alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomized controlled trial found it to be no less effective than CBT for adults with depression.[121]

#### mild depression, nonpregnant: low to moderate severity symptoms, partial impairment, no psychotic symptoms, no suicidal ideation, and no psychomotor retardation or agitation

<table>
<thead>
<tr>
<th>1st antidepressant</th>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>citalopram</strong>: 20 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
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<tr>
<td>OR</td>
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<tr>
<td><strong>escitalopram</strong>: 10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day</td>
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<td>OR</td>
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<tr>
<td><strong>fluoxetine</strong>: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 80 mg/day; doses &gt;20 mg/day may be given in 2 divided doses A delayed-release, once-weekly formulation is available for maintenance therapy.</td>
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<td>OR</td>
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<tr>
<td><strong>paroxetine</strong>: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 50 mg/day; 25 mg orally (controlled-release) once daily initially, increase gradually according to response, maximum 62.5 mg/day</td>
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<td>OR</td>
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<tr>
<td><strong>sertraline</strong>: 50 mg orally once daily initially, increase gradually according to response, maximum 200 mg/day</td>
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<td>OR</td>
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</tbody>
</table>
### Acute

- **desvenlafaxine**: 50 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day; doses >50 mg/day have not shown additional benefit

OR

- **duloxetine**: 40-60 mg/day orally initially given in 1-2 divided doses, increase gradually according to response, maximum 120 mg/day; doses >60 mg/day have not shown additional benefit

OR

- **levomilnacipran**: 20 mg orally once daily initially for 2 days, increase to 40 mg once daily, then increase gradually according to response, maximum 120 mg/day

OR

- **venlafaxine**: 75 mg/day orally (immediate-release) initially given in 2-3 divided doses, increase gradually according to response, maximum 225 mg/day; 75 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 225 mg/day

OR

- **bupropion hydrochloride**: 100 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 450 mg/day given in 2-3 divided doses; 150 mg orally (sustained-release) once daily initially, increase gradually according to response, maximum 400 mg/day given in 2 divided doses; 150 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 450 mg/day

OR

- **mirtazapine**: 15 mg orally once daily initially, increase gradually according to response, maximum 45 mg/day

OR

- **vilazodone**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
**Depression in adults**

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### Acute

**OR**

- **vortioxetine**: 5-10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

**The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.**

**Patients with mild to moderate depression do equally well with either cognitive behavioral therapy3[B]Evidence or an antidepressant.[122] 6[C]Evidence** An antidepressant may be preferable in some patients as it may offer a more rapid response than self-help or psychotherapy.

**Commonly used antidepressants include selective serotonin-reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone, vortioxetine).**

**The most commonly prescribed antidepressants, SSRIs and SNRIs, offer similar response rates and can be used first line as monotherapy in mild to moderate disease.[150] There is essentially no consistent evidence that any of the traditional antidepressants are superior to any other.[151] Choice of drug should also be based on patient preference, tolerability, and past evidence of effectiveness in the patient or a family member.**

**Combination psychotherapy and medication offers no demonstrated short-term advantage in this group. However, continued psychotherapy with antidepressant management is an effective option when continued through both acute and ongoing phases of treatment.[83]**

**Although the net result of antidepressant response is a significant reduction in suicidal ideation,[80] [87] there is some evidence of increased suicidal behavior in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[88] [89] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.[90] [91] The results of one large
Acute meta-analysis suggest that, in adults under the age of 25 years, the risk of both emergence and worsening of suicidality may be raised in weeks 3-6 of treatment (but not in weeks 1-2), which is later than has been suggested by other studies.[92]

» Determine antidepressant dose based on known target dose range. High-dose SSRI treatment for depression in patients refractory to medium-dose treatment is not recommended.[220] In a minority of patients, pharmacogenomic testing may indicate using a low-end or high-end dose depending on genotype. On balance, there is no evidence to support routinely increasing the dose beyond the established dose range.[93]

» Follow up patients 1-2 weeks after initiating therapy, then monthly for the next 12 weeks. If you prefer systematic evaluation, use the Patient Health Questionnaire-9 (PHQ-9) to assess changes in symptom severity. A 50% decrease in symptom score constitutes an adequate response, and a 25% to 50% change in symptom score may indicate the need to modify treatment.

» Continue successful antidepressant treatment for 9-12 months following remission;[102] [103] however, some physicians recommend that patients with frequent recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.

1st psychotherapy

» Psychotherapy is also considered a first-line option in mild to moderate depression. Psychotherapy appears to have a positive impact on the quality of life of patients with depression, beyond measurable reductions in depressive symptom severity.[152] Mild depression treated with psychotherapy may be less likely to progress to severe depression.[153] Psychoeducation alone can achieve remission for some patients.[154]

» Therapists often use a combination of cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) or problem-solving therapy.[114] [115] [116] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[117] IPT is useful only if the patient has the capacity for
Depression in adults

Acute

psychological insight and is committed to longer-term therapy.[118] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. Time-limited psychodynamic therapy has also gained empirical support as a treatment for major depression.[155]

1st **supportive interventions**

» Self-help books are popular and bibliotherapy has demonstrated better efficacy than no treatment at all.[156] Cognitive bibliotherapy has shown outcomes similar to those of psychotherapy.[222] There are no data on bibliotherapy alone. Two recommended texts are: "Feeling good: the new mood therapy" by Davis D. Burns, and "Managing anxiety and depression: a self-help guide" by Nicholas Holdsworth and Roger Paxton.[223] [224] [225] The former is based on the cognitive behavioral therapy approach. One meta-analysis found a large improvement at 4 weeks, but the participants appeared to have a very high educational level.[226]

» Yoga interventions may have a beneficial effect on depressive disorders, but there are significant variations in interventions, reporting, and feasibility.[157] [158] [Evidence]

» Other supportive interventions include relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture.[126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [136] [137] [138] [139] [140] In nonremitted patients, higher remission rates were observed in a higher-dose exercise group plus continuation of serotonin norepinephrine-reuptake inhibitor treatment compared with low-dose exercise plus selective serotonin-reuptake inhibitors.[159] Conversely, cessation of exercise may worsen depressive symptoms.[160] [161]

1st **computer-based interventions**

» Evidence supports the efficacy of computer-based cognitive behavioral therapy,[141] [142] [143] [144] [145] [146] problem-solving therapy,[147] [148] and stress management.[149] However, high withdrawal rates are common.

2nd **switch to alternative antidepressant**

» If the response to first-line therapy is inadequate, consider switching to an alternative antidepressant.[94] [95] By the end of four different medication trials, 60% to 70% of
Acute patients are likely to respond to treatment. Switching may be appropriate if no improvement in symptoms has occurred within the first 2 weeks of treatment;[96] [97] however, early response may be, but is not necessarily, a reliable indicator of continued response.[98] [99] Continue treatment if there has been some improvement for at least the full 6-8 weeks, but do not continue prescribing a drug providing inadequate benefit indefinitely. Of note, in patients with no initial improvement to treatment with fluoxetine, one study showed the likelihood of converting to a positive response decreased the longer patients remained unimproved.[100]

» Consider a change in drug class; if a patient was on a selective serotonin-reuptake inhibitor, then try a serotonin norepinephrine-reuptake inhibitor. If treatment was not tolerated due to adverse effects, retry with an agent with fewer or different adverse effects. If an agent is switched, resume weekly follow-up until a response is apparent. Continue with psychotherapy if applicable, as psychotherapy may reduce the risk of mild depression progressing to severe depression.[153]

» Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. The timeframe required for safely switching depends on various factors, including the pharmacokinetic properties of the drugs and possible interactions between them, as well as patient characteristics such as age, sensitivity to adverse effects, and the capacity to wait to begin a new course of treatment. In some situations, it is possible to give both drugs for a short period of time while the changeover is occurring; however, this should only be done under specialist guidance. In other cases, it is safer to take a more conservative approach. This involves slowly tapering the dose of the first drug before stopping it, and then waiting a period of time before starting the second drug (known as a washout period, which is usually five half-lives of the first drug). Drugs with longer half-lives (e.g., fluoxetine) require longer washout periods (e.g., up to 5-6 weeks) when combined with a drug with which the combination is contraindicated (e.g., monoamine oxidase inhibitors with fluoxetine). Specific recommendations for switching from one antidepressant to another, along with suitable washout periods, are available and local guidance should be consulted. When in doubt, in the absence of such guidelines, as a general
## Acute

principle perform a drug interaction check to be sure there are no absolute contraindications, and then "start low and go slow" until safety can be ascertained.

- Continue successful antidepressant treatment for 9-12 months following remission;[102] [103] 2[A]Evidence however, some physicians recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.

- If there is an inadequate response to two (or more) full-dose and duration antidepressants, the patient's depression might be considered treatment resistant or refractory, and warrants a more complex approach.

### 3rd St John’s wort

- St John’s wort is a herb thought to work by inhibiting serotonin reuptake or decreasing cell surface serotonin receptors.

- It is considered to be effective in mild to moderate depression.[162] [163] 8[C]Evidence It may also be used as an alternative therapy (as monotherapy only) if there is no response to first- and second-line treatments.

- Has an encouraging safety profile; however, numerous reports indicate the possibility of clinically significant drug-drug interactions, which must be taken into account before prescribing.[227] [165]

- Must not be given concomitantly with other antidepressants due to the risk of serotonin syndrome.

- Formulations may vary; refer to product literature for dosing guidelines.

<table>
<thead>
<tr>
<th>treatment-resistant/refractory depression</th>
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<tbody>
<tr>
<td>1st reassess and switch to alternative antidepressant or try combination therapy</td>
</tr>
</tbody>
</table>

### Primary options

- citalopram: 20 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day

OR
## Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th><strong>escitalopram</strong>: 10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td><strong>fluoxetine</strong>: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 80 mg/day; doses &gt;20 mg/day may be given in 2 divided doses A delayed-release, once-weekly formulation is available for maintenance therapy.</td>
</tr>
<tr>
<td>OR</td>
<td><strong>paroxetine</strong>: 20 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 62.5 mg/day</td>
</tr>
<tr>
<td>OR</td>
<td><strong>sertraline</strong>: 50 mg orally once daily initially, increase gradually according to response, maximum 200 mg/day</td>
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<tr>
<td>OR</td>
<td><strong>desvenlafaxine</strong>: 50 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day; doses &gt;50 mg/day have not shown additional benefit</td>
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<td>OR</td>
<td><strong>duloxetine</strong>: 40-60 mg/day orally initially given in 1-2 divided doses, increase gradually according to response, maximum 120 mg/day; doses &gt;60 mg/day have not shown additional benefit</td>
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<tr>
<td>OR</td>
<td><strong>levomilnacpran</strong>: 20 mg orally once daily initially for 2 days, increase to 40 mg once daily, then increase gradually according to response, maximum 120 mg/day</td>
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<tr>
<td>OR</td>
<td><strong>venlafaxine</strong>: 75 mg/day orally (immediate-release) initially given in 2-3 divided doses</td>
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</table>
**Acute**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>doses, increase gradually according to response, maximum 225 mg/day; 75 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 225 mg/day</strong></td>
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<td>OR</td>
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<tr>
<td><strong>mirtazapine:</strong> 15 mg orally once daily initially, increase gradually according to response, maximum 45 mg/day</td>
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<td>OR</td>
<td></td>
</tr>
<tr>
<td><strong>vilazodone:</strong> 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
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<td>OR</td>
<td></td>
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<tr>
<td><strong>vortioxetine:</strong> 5-10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day</td>
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<td>OR</td>
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<tr>
<td><strong>amitriptyline:</strong> 25 mg orally once daily at bedtime initially, increase gradually according to response, maximum 150-300 mg/day (may give in divided doses)</td>
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<td>OR</td>
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<tr>
<td><strong>desipramine:</strong> 50-75 mg orally once daily at bedtime initially, increase gradually according to response, maximum 200-300 mg/day (may give in divided doses)</td>
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</tbody>
</table>
Depression in adults

### Treatment

**Acute**

- **doxepin**: 25-75 mg orally once daily at bedtime initially, increase gradually according to response, maximum 150-300 mg/day (may give in divided doses)

OR

- **imipramine**: 25-75 mg orally once daily at bedtime initially, increase gradually according to response, maximum 150-300 mg/day (may give in divided doses)

OR

- **nortriptyline**: 25-50 mg orally once daily at bedtime initially, increase gradually according to response, maximum 150 mg/day (may give in divided doses)

The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.

The majority of patients with depression do not respond adequately to their first antidepressant trial, but a substantial proportion of those will respond to a second antidepressant.[166] The general consensus is to consider a depressive illness that has not responded to two antidepressant trials of adequate dose and duration (preferably using two antidepressants with distinct mechanisms of action) to be treatment resistant or refractory.[167]

Reassessment can be useful after an apparently failed course of treatment, as some of the residual symptoms of depression (e.g., social avoidance, sleep/wake reversal, a demoralized attitude) can reflect behavioral adaptations to depression, rather than the disease itself. In such cases, symptoms may best be corrected through behavioral intervention or psychotherapy rather than a new medication trial. With intermittent, brief follow-up visits it is also easy to miss mood-cycling that may occur between sessions that would indicate a bipolar spectrum disorder rather than pure major depression. Consider diagnostic re-evaluation, or whether there may have been issues around adherence with treatment, or if factors such as substance abuse, medication adverse effects, or medical illness may have interfered with treatment.

Assuming major depressive disorder continues to be the most salient clinical problem,
Alternative options for treatment-resistant/refractory depression within the antidepressant class include monotherapy with a third (or fourth or fifth) selective serotonin-reuptake inhibitor (SSRI), serotonin norepinephrine-reuptake inhibitors (SNRI), or an atypical agent (e.g., bupropion, mirtazapine, vilazodone, vortioxetine). Combined antidepressant therapy (i.e., an SSRI or SNRI plus bupropion or mirtazapine) may be indicated as a way of making optimal use of adverse effects (e.g., adding mirtazapine to an SNRI to facilitate sleep, or bupropion to an SSRI to try to improve sexual functioning); however, the evidence has not consistently supported a synergistic effect of combined antidepressants in alleviating depression.[169] [170] [171] [172] There is some evidence that failure on one or several antidepressants does not preclude later success.[173] [166] By the end of four different medication trials, 60% to 70% of patients are likely to respond to treatment. Although the general rule of thumb is to give antidepressants for at least 6-8 weeks, if there is no improvement at all in the first 2 weeks, switching may be appropriate at that point.[174]

When selecting a third (or fourth or fifth) medication to switch to, consider not only another SSRI, SNRI, or atypical agent, but also a tricyclic antidepressant (TCA) (e.g., amitriptyline, desipramine, doxepin, imipramine, or nortriptyline). Historically the first-line pharmacotherapy for depression, TCAs have fallen somewhat out of favor because of their adverse effects, the need for gradual dose increases, and their potential lethality in overdose. However, they remain effective and useful for many patients. Dose TCAs according to therapeutic blood monitoring. For most TCAs there is a minimum therapeutic level; for nortriptyline, uniquely, there is a therapeutic window delineating a range of effective levels.

Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. The timeframe required for safely switching depends on various factors, including the pharmacokinetic properties of the drugs and possible interactions between them, as well as patient characteristics such as age, sensitivity to adverse effects, and the capacity to wait to begin a new course of treatment. In some situations, it is possible to give both drugs for a short period of time while the changeover is occurring; however, this should...
Depression in adults

**Treatment**

<table>
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<th>Acute</th>
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| Only be done under specialist guidance. In other cases, it is safer to take a more conservative approach. This involves slowly tapering the dose of the first drug before stopping it, and then waiting a period of time before starting the second drug (known as a washout period, which is usually five half-lives of the first drug). Drugs with longer half-lives (e.g., fluoxetine) require longer washout periods (e.g., up to 5-6 weeks) when combined with a drug with which the combination is contraindicated (e.g., monoamine oxidase inhibitors with fluoxetine). Specific recommendations for switching from one antidepressant to another, along with suitable washout periods, are available and local guidance should be consulted. When in doubt, in the absence of such guidelines, as a general principle perform a drug interaction check to be sure there are no absolute contraindications, and then "start low and go slow" until safety can be ascertained.  

" » Continue successful antidepressant treatment for 9-12 months following remission;[102] [103] 2[A]Evidence however, some physicians recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.  

plus consider augmentation therapy

Treatment recommended for ALL patients in selected patient group

**Primary options**

- **lithium**: consult specialist for guidance on dose
- **OR**
- **aripiprazole**: consult specialist for guidance on dose
- **OR**
- **olanzapine/fluoxetine**: consult specialist for guidance on dose
- **OR**
- **brexpiprazole**: consult specialist for guidance on dose

» The specific drug regimens above are examples of commonly used regimens only.
Consult local guidance for other examples and preferred options.

» The addition of an atypical antipsychotic to an antidepressant has been historically controversial;[178] [179] however, augmentation with some agents is becoming more common practice and may improve outcomes.[180] [181] Second-generation antipsychotic medications used in combination with antidepressants demonstrate efficacy and their use is becoming widespread.[182] Some studies show that combinations of antidepressants with other classes of medication are better than just a combination of different antidepressants alone.[176]

» In patients who have not responded to conventional antidepressants, lithium augmentation remains the best evidence-based approach; however, it is ideally initiated by a psychiatrist because of its narrow therapeutic index and risks of inadvertent toxicity from excessive dosing and drug-drug interactions. While these limitations make lithium unwieldy as a first-line treatment, evidence has emerged from one Finnish cohort study suggesting that lithium monotherapy is not only effective at preventing rehospitalization after severe depression, but is also more effective on its own than when combined with antidepressants.[177]

» Olanzapine may also be used. A commercially available olanzapine/fluoxetine combination has been shown to be superior to fluoxetine monotherapy and olanzapine monotherapy in producing early improvement in patients who have not responded to an antidepressant trial.[180]

» Aripiprazole, which the Food and Drug Administration (FDA) has approved for antidepressant augmentation, was found to be slightly more effective as augmentation than switching to a different antidepressant in US military veterans with treatment-resistant depression.[181]

» Brexpiprazole, a novel serotonin-dopamine activity modulator, is approved by the FDA as an adjunctive treatment for major depressive disorder,[183] although the evidence for its efficacy derives from a relatively small number of studies.[184] Weight gain and akathisia are among the most commonly reported adverse effects, and small effects on glucose and lipids have also been noted.[185] While some benefit has been demonstrated in meta-
Depression in adults

Treatment

Acute

analysis of clinical trial data, it is unclear whether benefits outweigh risks in people without psychosis.[178] Other augmentation strategies used by specialists include thyroid hormone, modafinil, ketamine, and pindolol.[186] [187] [188]

plus psychotherapy or other nonpharmacologic treatment

Treatment recommended for ALL patients in selected patient group

» Check and ensure that the patient has started psychotherapy if multiple pharmacologic agents have been unsuccessful.

» Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[105] [106]

» In addition to pharmacotherapeutic strategies, cognitive behavioral therapy (CBT) has shown greater efficacy than pharmacologic placebo across levels of severity.[107] Treatment response to CBT is comparable with antidepressant response in some studies.[108] Staged treatment trials suggest that CBT may be particularly beneficial when used during the continuation phase of treatment; CBT reduces the risk of relapse/recurrence at least as well as, and perhaps better than, antidepressant continuation.[109] [110] [111] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[112] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[113]

» Therapists often use a combination of CBT and interpersonal psychotherapy (IPT) or problem-solving therapy (PST).[114] [115] [116] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[117] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[118] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. PST focuses on training in adaptive problem-solving attitudes and skills.[115] [119]

» Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[120]
### Treatment

#### Depression in adults

**Acute**

» Behavioral activation is a less cerebral, more behavioral alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomized controlled trial found it to be no less effective than CBT for adults with depression.[121]

2nd **monoamine oxidase inhibitor (MAOI)**

**Primary options**

» **isocarboxazid**: 10 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day given in 2-4 divided doses

OR

» **phenelzine**: 15 mg orally three times daily initially, increase gradually according to response, maximum 90 mg/day; reduce dose gradually once maximum benefit is achieved to 15 mg once daily or on alternate days

OR

» **selegiline transdermal**: 6 mg/24 hours patch once daily initially, increase gradually according to response, maximum 12 mg/24 hours

OR

» **tranylcypromine**: 30 mg/day orally initially given in 2-3 divided doses, increase gradually according to response, maximum 60 mg/day

The specific drug regimens above are examples of commonly used regimens only. Consult local guidance for other examples and preferred options.

MAOIs inhibit monoamine oxidase, causing an increase in monoamine neurotransmitters (e.g., serotonin, epinephrine, and dopamine). MAOIs are rarely used as they have many drug-drug and drug-food interactions, and should not be used in patients with hypertension. They are generally not used in primary care, and should not be used without consulting a psychiatrist first.

Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. The timeframe required...
for safely switching depends on various factors, including the pharmacokinetic properties of the drugs and possible interactions between them, as well as patient characteristics such as age, sensitivity to adverse effects, and the capacity to wait to begin a new course of treatment. In some situations, it is possible to give both drugs for a short period of time while the changeover is occurring; however, this should only be done under specialist guidance. In other cases, it is safer to take a more conservative approach. This involves slowly tapering the dose of the first drug before stopping it, and then waiting a period of time before starting the second drug (known as a washout period, which is usually five half-lives of the first drug). Drugs with longer half-lives (e.g., fluoxetine) require longer washout periods (e.g., up to 5-6 weeks) when combined with a drug with which the combination is contraindicated (e.g., monoamine oxidase inhibitors with fluoxetine). Specific recommendations for switching from one antidepressant to another, along with suitable washout periods, are available and local guidance should be consulted. When in doubt, in the absence of such guidelines, as a general principle perform a drug interaction check to be sure there are no absolute contraindications, and then "start low and go slow" until safety can be ascertained.

» Continue successful antidepressant treatment for 9-12 months following remission.[102][103] Evidence however, some physicians recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require indefinite therapy.

plus psychotherapy or other nonpharmacologic treatment

Treatment recommended for ALL patients in selected patient group

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Depression in adults

Treatment

**Acute**

Staged treatment trials suggest that CBT may be particularly beneficial when used during the continuation phase of treatment; CBT reduces the risk of relapse/recurrence at least as well as, and perhaps better than, antidepressant continuation.[109] [110] [111] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[112] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[113]

- Therapists often use a combination of CBT and interpersonal psychotherapy (IPT) or problem-solving therapy (PST).[114] [116] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[117] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[118] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. PST focuses on training in adaptive problem-solving attitudes and skills.[115] [119]

- Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[120]

- Behavioral activation is a less cerebral, more behavioral alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomized controlled trial found it to be no less effective than CBT for adults with depression.[121]

3rd electroconvulsive therapy (ECT)

- ECT may be an option for those who have not responded to, or cannot tolerate, antidepressants. The transient impact on memory and cognition, which may reduce functioning during active treatment, make ECT less desirable for milder cases. The effects of ECT generally last only a few weeks, so pharmacotherapy is necessary to sustain its effects or act as maintenance therapy.

- ECT is performed under general anesthesia, 2 or 3 times a week for a total of 6-12 treatments. Improvement is usually noted after several treatments.[221]
Acute

» The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments,[76][77] meaning that it is one of the safer procedures performed under general anesthetic. The risk of death may be increased in patients with coronary heart disease, due to a theoretical increased risk of ischemia during the induced seizure. Short-term cognitive adverse effects (e.g., amnesia) are common,[78] and a significant proportion of patients report persistent memory loss following ECT.

pregnant

1st antidepressant or electroconvulsive therapy (ECT)

» Severe episodes: ECT is the treatment of choice when a depressive illness puts the fetus at risk either due to poor maternal self-care or suicide. There is no known risk to the fetus.[207][208]

» Moderate to severe episodes: there is little consistent controlled trial evidence that antidepressants should be contraindicated during pregnancy; the risk to the fetus from the potentially harmful effects of the mother’s untreated depression on her health apparently outweighs any detectable risk to the fetus from antidepressants.[209][190][191]

» Mild episodes: treat mild depression in pregnancy as you would any other, perhaps with a slightly higher threshold for using medication than you would with a nonpregnant patient. There is little consistent controlled evidence that antidepressants should be contraindicated during pregnancy, but the risk/benefit balance may tip in favor of nonpharmacologic therapies, particularly because many patients may have reservations about using medication when pregnant.

» Risks from antidepressant use are most apparent in the neonatal period. A newborn exposed to antidepressants in utero may potentially undergo a discontinuation syndrome similar to that of adult patients who abruptly stop antidepressants.[201] Despite the lack of consistent evidence of harmful effects of antidepressants to fetal and infant health and development, caution is required. Updated information about potential harms from antidepressants and other pharmaceuticals can be found at various resources. [MotherToBaby]

plus psychotherapy
### Acute

Treatment recommended for ALL patients in selected patient group

- Cognitive behavioral therapy (CBT) is associated with a robust moderate treatment effect for major depressive disorder during pregnancy. Interpersonal psychotherapy also appears to have a treatment effect, but to a lesser extent than CBT.[210]
### Ongoing Treatment

<table>
<thead>
<tr>
<th>Treatment responsive</th>
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<tbody>
<tr>
<td>1st maintenance antidepressant therapy</td>
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<tr>
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<table>
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<tr>
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<tr>
<td>- Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[105] [106]</td>
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<tr>
<td>- Continued psychotherapy with antidepressant management is an effective option when continued through both acute and ongoing phases of treatment.[83] Staged treatment trials suggest that cognitive behavioral therapy (CBT) may be particularly beneficial when used during the continuation phase of treatment; CBT reduces the risk of relapse/recurrence at least as well as, and perhaps better than, antidepressant continuation.[109] [110] [111]</td>
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» Mild depression treated with psychotherapy may be less likely to progress to severe depression.[153]

<table>
<thead>
<tr>
<th>recurrent episode</th>
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<tr>
<td>1st</td>
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<td>repeat of remission-inducing regimen or long-term therapy</td>
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<tr>
<td>» Recurrent episodes of major depression should be treated with the same antidepressant that previously led to remission, provided that the recurrence did not occur while under adequate maintenance treatment with such medication.</td>
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<tr>
<td>» Consider maintenance therapy for at least 3-5 years or lifetime maintenance treatment for patients on their third episode of depression. Patients with a first recurrence and risk factors for further recurrences (i.e., family history of bipolar disorder, recurrence within 1 year, onset in adolescence, severe depression or suicidal attempt, and sudden onset of symptoms) may also benefit from long-term maintenance therapy. The selection and success of these treatments depends on the type and severity of depressive symptoms, but most often relies on trial and error.</td>
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<tr>
<td>plus</td>
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<tr>
<td>psychotherapy</td>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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» Psychotherapy in patients who suffer from recurrent episodes may be well aimed if it addresses the despair patients often feel when they see recovery as only a temporary respite from suffering, and if it educates patients about ways to cope with and possibly prevent recurrences.
Emerging

New antidepressants

A variety of new and older reformulated agents are under development; unlike traditional antidepressants, they do not all have a primary mechanism of action involving monoaminergic neurotransmission.\[228\] While vortioxetine has been approved for major depressive disorder since 2013, there is preliminary evidence that it is effective for patients who have comorbid severe anxiety.\[230\] Psilocybin, a psilocybin drug, has received breakthrough therapy designation from the Food and Drug Administration (FDA) for treatment-resistant depression.\[231\] Agomelatine, a melatonin receptor agonist and serotonin 5-HT2c receptor antagonist, has been found to be effective and is available in Europe.\[232\] Another antidepressant available in Europe, reboxetine, is not approved by the FDA for use in the US, at least in part due to the results of one meta-analysis that suggest the drug is inferior to selective serotonin-reuptake inhibitors, and is more strongly associated with adverse events.\[233\]

Esketamine nasal spray

In March 2019 the FDA approved esketamine nasal spray, to be used in conjunction with an oral antidepressant, for treatment-resistant depression in adults. Administration of the drug is only available through a restricted distribution system, under a Risk Evaluation and Mitigation Strategy (REMS) in which both the prescriber and patient sign a patient enrollment form. The drug must be self-administered by the patient, who is supervised by a health care provider in a certified medical office, and the patient monitored for at least 2 hours because of the risk of the sedation, difficulty with attention, judgment and thinking (dissociation), suicidal thoughts and behaviors, and the potential for drug misuse. Be aware that patients with poorly controlled hypertension or pre-existing aneurysmal vascular disorders may be at increased risk for adverse cardiovascular or cerebrovascular effects. The efficacy of esketamine was evaluated in two short-term (four-week) clinical trials and one longer-term maintenance-of-effect trial. In one of the short-term studies, esketamine nasal spray demonstrated statistically significant effect compared with placebo on the severity of depression, and some effect was seen within 2 days.\[234\] The other short-term trial did not show statistically significant effectiveness, but the authors noted that the treatment effect for esketamine nasal spray exceeded what has been considered clinically meaningful for approved antidepressants versus placebo.\[235\] In the longer-term maintenance-of-effect trial, esketamine plus an oral antidepressant resulted in a statistically significantly longer time to relapse of depressive symptoms compared with placebo nasal spray plus an oral antidepressant.\[236\] The most common side effects were disassociation, dizziness, nausea, sedation, vertigo, decreased feeling or sensitivity (hypoesthesia), anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.\[237\] However, esketamine did not impair driving performance in one small double-blind, placebo-controlled study. The European Medicines Agency approved esketamine nasal spray for this indication in October 2019.

Transcranial magnetic stimulation (TMS)

Data support an antidepressant effect of high-frequency repetitive TMS administered to the left prefrontal cortex,\[238\] and guidelines for best practice are being developed.\[239\] A bank of capacitors is rapidly discharged into an electric coil to produce a magnetic field pulse. When the coil is placed near the patient’s head, the magnetic field penetrates the brain and induces an electric field in the cerebral cortex. An electric field of sufficient intensity will depolarize cortical neurons, generating action potentials and leading to biological effects.\[238\] The absence of psychosis and younger age may predict success.\[238\] Review of literature has found inconsistent evidence of a benefit in depression.\[240\] \[241\] \[242\] \[243\] and some evidence of a synergistic effect with concurrent antidepressant treatment.\[244\] In a durability study, TMS therapy has been shown to have durable effects and may be successfully used as an intermittent rescue strategy to prevent impending relapse.\[245\] Based on a small sample size, it appears to be safe and effective in pregnancy, although data are limited and further controlled studies are warranted.\[246\] Work is ongoing to establish whether variation in treatment parameters might affect outcomes.\[247\] Other evidence suggests that TMS is no different from sham TMS treatment in patients with depression.\[248\] Large-scale studies are needed.\[249\]

Nonsteroidal anti-inflammatory drugs (NSAIDs)
Dealing with Depression in Adults

### Treatment

A systematic review and meta-analysis of the efficacy of NSAIDs in depression suggests they may be effective (particularly celecoxib) and safe for this indication; however, further work is needed to determine in which patients NSAIDs might be most effective.[250]

**Vagus nerve stimulation (VNS)**

VNS entails stimulation of the left cervical vagus nerve, using a commercial device termed the VNS Therapy System.[251] The generator is programmed to deliver mild electric pulses in continuous cycles, typically with 30 seconds of stimulation followed by 5 minutes off.[252] VNS has been approved in the US for the adjunctive long-term treatment of chronic depression for patients aged ≥18 years, who are experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments.[253] One meta-analysis found no conclusive evidence for the efficacy of VNS in the treatment of depression.[254]

**Deep brain stimulation (DBS)**

DBS of structures in the forebrain has had promising effects against treatment-resistant depression in a small group of individuals, but it is far from routine or low risk.[255] Results are limited by small sample size and insufficient randomized control data.[256] [257]

**Transcranial direct current stimulation (tDCS)**

Similar to TMS in the localization of treatment and tolerability but uses current rather than magnetic field. While the effect size was similar to that of TMS in some studies,[258] results from other trials have been mixed.[259] tDCS appears to perform better for acute depression than for treatment-resistant depression and seems to be a relatively safe option, with only minor adverse effects noted to-date.[260]

**Methylphenidate and thyroid hormone**

The benefits of methylphenidate and thyroid hormone as single or co-therapy remain controversial.[261] [262] [263] [264] [265]

**Nutraceuticals**

Adjuvant use of pharmaceutic-grade nutrients, such as S-adenosylmethionine (SAMe), acetylthymine, methylfolate, omega-3 fatty acids, vitamin D, and others, has been found to be effective in improving antidepressant response in some studies, and adds little if any risk to the patient.[266] [267] [268] [269] Folic acid has been of particular interest due to the observation that patients with depression have lower levels of serum folate than people without depression, including nondepressed psychiatric patients.[50] Folate supplementation may also be effective when added to standard antidepressant treatment in patients who are treatment naive or treatment resistant; however, results have been inconsistent.[50] [270] One 2×2 factorial randomized clinical trial of multinutrients (omega-3 fatty acids, selenium, folic acid, and vitamin D3 plus calcium), therapy (group or individual), or their combination, given to overweight patients with subsyndromal depressive symptoms showed that multinutrients did not reduce episodes of major depressive disorder over the 1 year.[271]

**N-methyl-D-aspartate (NMDA)-specific agents**

Ketamine is one of a number of NMDA-specific agents shown to have some success in alleviating depression,[272] however, the data are too limited to make it a standard treatment for depression.[273] In case reports, case series, and select trials ketamine has been shown to have a rapid effect in the reduction of scores on a number of depression scales.[274] [275] In a multicenter trial, intravenous ketamine demonstrated sustained efficacy over a 2-week period.[276] A systematic review of 60 articles looking at side effects in adults with depression treated with single and repeated doses of ketamine found that acute side effects were common, and were more likely to occur in patients given intravenous ketamine. The majority of side effects resolved shortly after drug administration. They included psychiatric (most commonly anxiety), psychotomimetic, cardiovascular, and neurologic effects. The most common somatic effects were headache,
dizziness, dissociation, elevated blood pressure, and blurred vision.\[277\] However, its safety and efficacy for long-term use remain unknown.\[278\] \[279\] Repeated use of ketamine in other patient groups has been linked to urological and liver toxicity, cognitive deficits, and dependency.\[277\]

**Pharmacogenetics**

The emergence of fast and affordable genetic assays has led to the increasingly widespread use of genetic testing to guide selection of antidepressant medications for depression. The tests generally convey two kinds of information: some of the assays detect allelic variants of key enzymes that have proven associations with variations in treatment response; the majority delineate the variant hepatic drug-metabolizing enzymes in an individual.\[280\] This information does not reveal which medications an individual may find effective but rather, whether a person might require high doses of a medication (being a rapid metabolizer who excretes the drug before it can adequately perfuse the brain), or low doses (for a slow metabolizer who may find recommended drug doses to have intolerable side effects). These tests may improve outcome,\[281\] but have not proven to be cost effective in practice. Pharmacogenomic analysis is not yet recommended for routine use.\[86\]
Recommendations

Monitoring

Initial

- Nonadherence to medication is common, and appears to be associated with a number of adverse clinical outcomes, including increased severity of depression, and increased risk of relapse and hospitalization. One half or more of patients receiving antidepressants fail to take them at an adequate dose for an adequate duration.[300] [301] During the 8- to 12-week initiation and titration phase, the first 2 weeks of drug therapy has the greatest discontinuation risk.
- Help patients to continue medication therapy by offering a timely response to adverse effects and by maintaining close contact. Beyond their utility in the diagnostic work-up, features of the history, exam, and laboratory studies can prove vital in monitoring for, and preventing adverse effects from, treatment.[302] Follow up with patients, in person or by telephone, within the first 2 weeks to address adverse effects, suicidality, and acceptance of medication taking, and to reinforce educational messages. Telephone follow-up by a trained nurse is also effective,[303] as is text messaging.[304]
- There is emerging evidence that a brief psychosocial intervention addressing barriers to antidepressant treatment (the Treatment Initiation and Participation Programme), delivered in three 30-minute sessions in the first 6 weeks of antidepressant treatment, may improve rates of treatment adherence in older adults in primary care.[305]

Continuation and maintenance

- Depending on the speed, stability, and adequacy of response, treatment of depression may require close follow-up for up to 1 year in order to adjust or augment therapy.
- During the 12-week maintenance phase, monitor patients monthly in person or by telephone. It is important to continue assessing adherence, suicidality, and adverse effects. Once symptom remission has been achieved, patients should continue on the current regimen for a minimum of 9 to 12 months.[102] [103] [2][Evidence Educate patients and their families to self-assess for symptoms and risk for recurrent episodes, and continue to rescreen patients at regularly scheduled appointments.
- Use the Patient Health Questionnaire-9 (PHQ-9) to objectively assess changes in symptom severity. A 50% decrease in symptom score constitutes an adequate response, and a 25% to 50% change in symptom score may indicate the need to modify treatment.
- Disease management “care pathways” address the multiple needs of patients with depression. Programs have been shown in multiple practice settings to improve care. Key elements of the care pathways can include coordination of care by care managers, provider education, structured systematic assessment of patient response to treatment with feedback to the provider, stepped-care referrals for psychiatric consultation, in-clinic psychiatric care, nurse-administered telephone support, text messaging, and education calls or peer support.[66] [303] [306] [307] [308] [309] [310] [311] [312] [313] [314] [304] There may be an increasing role for self-help and self-guided interventions such as behavioral activation strategies and internet-based therapy;[315] [316] however, patients with a lower educational level may be at increased risk of symptom deterioration with internet-based guided-self-help than patients with higher education.[317]

Patient instructions

Anyone who is experiencing symptoms of depression should be evaluated by a doctor. Although individuals with depression often feel that nothing can help them, effective treatments are available. Medications and psychotherapy are the most common treatments. There are many different types of antidepressant medications. These medications may take several weeks before they become effective and should be taken for many months to prevent symptoms from coming back. Medications are helpful for
patients with mild, moderate, or severe depression and the physician or psychiatrist will help decide which one suits the patient best.

Psychotherapy or talk therapy also helps most patients with depression. Talk therapy helps the patient explore and change the thoughts, attitudes, and relationship problems associated with depression. Mild or moderate depression can be treated effectively with psychotherapy alone. Severe depression requires both psychotherapy and antidepressant medications.

Patient education should include warnings about the potential problems associated with the abrupt discontinuation of antidepressants.
# Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>sexual adverse effects of selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)</td>
<td>short term</td>
<td>medium</td>
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<td>Treatment options include: switching to a drug with a different mechanism of action (e.g., bupropion or mirtazapine or trazodone) or, in the absence of contraindications, considering augmentation with sildenafil.[291][292] The addition of bupropion or trazodone to SSRI therapy may also be helpful.[293]</td>
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<tr>
<td>risk of self-injurious behavior</td>
<td>short term</td>
<td>medium</td>
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<tr>
<td>Children, adolescents, and young adults may experience a transient increase in risk for self-injury, most severe with rapid escalation in dosing.[89]</td>
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<tr>
<td>undesired weight gain from antidepressants</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Weight gain is most common with mirtazapine but can also be seen with SSRIs, venlafaxine, and tricyclic antidepressants. Patient may be switched to bupropion.</td>
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<tr>
<td>agitation or excessive activation from antidepressants</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Patient may be switched to another SSRI or a low-dose tricyclic antidepressant or mirtazapine may be added. Clinicians may consider offering a short course of benzodiazepines, starting at the lowest possible effective dose, to counter short-term agitation associated with SSRI initiation.</td>
<td></td>
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<tr>
<td>unmasking mania</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>As many as 1 in 5 patients diagnosed with depression may later go on to experience mania, hence convert to a bipolar disorder diagnosis; the best predictor is a family history of bipolar disorder.[294] Depressed patients with undiagnosed bipolar affective disorder may convert to frank mania if they receive antidepressant medication. Ask patients about a prior history of manic episodes (e.g., periods of days to weeks marked by unusually high energy, euphoria, insomnia, hyperactivity, or impaired judgment) before starting antidepressant therapy. Patients who develop manic or hypomanic symptoms after starting an antidepressant should be evaluated by a psychiatrist. Frank mania suggests bipolar illness and should prompt discontinuation of the antidepressant and initiation of a mood stabilizer, preferably under psychiatric supervision. Early initiation of mood-stabilizer drug therapy in bipolar disorder is important.[295]</td>
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<tr>
<td>mania due to antidepressant withdrawal</td>
<td>short term</td>
<td>low</td>
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<tr>
<td>Antidepressant-withdrawal mania or hypomania is an unusual event but may occur with almost any drug after sudden withdrawal, tapered discontinuation, or a decrease in dose.[296] The syndrome may be self-limiting, may abate with the reinstitution of the antidepressant, or may require antimanic treatment. Mood stabilizers do not necessarily protect against the syndrome.[297]</td>
<td></td>
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<tr>
<td>antidepressant discontinuation syndrome</td>
<td>short term</td>
<td>low</td>
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Follow up

Complications | Timeframe | Likelihood
--- | --- | ---
It occurs after abrupt discontinuation of an antidepressant medication that was taken for at least 6 weeks. Typical symptoms include influenza-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal.

risk of suicide with SSRI treatment | variable | low

The use of SSRIs may be associated with an increased risk of suicidal behavior in patients <25 years old and reduced risk in adults >25 years old.[65] [298] [299]

Prognosis

Complete remission of symptoms and return to normal functioning are the therapy goals. For patients in their first episode of depression, treatment to remission may take up to several months and should be continued for a minimum of 9 to 12 months after remission.[102] [103] [2(A)Evidence For patients who have had recurrent episodes, or in whom relapse or recurrence would likely convey a high risk, evidence supports prolonged antidepressant treatment.[103]

Depression recurs in about one third of patients within 1 year of discontinuing treatment and in >50% of patients during their lifetime.[11] Evidence that antidepressants can prevent relapse is unclear.[103] [114] After 15 years, 87% will experience a recurrence. For patients with 3 recurrent depressive episodes, many experts advocate long-term maintenance therapy.
Diagnostic guidelines

International

Perinatal depression: preventive interventions  [60]
Published by: US Preventive Services Task Force  Last published: 2019

Screening for perinatal depression  [61]
Published by: American College of Obstetricians and Gynecologists  Last published: 2018

Screening for depression in adults  [58]
Published by: US Preventive Services Task Force  Last published: 2016

Practice guideline for the psychiatric evaluation of adults  [62]
Published by: American Psychiatric Association  Last published: 2015

Recommendations on screening for depression in adults (for clinicians and policy makers)  [59]
Published by: Canadian Task Force on Preventive Health Care  Last published: 2013
# Treatment guidelines

## International

<table>
<thead>
<tr>
<th>Title</th>
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<th>Last published</th>
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<tbody>
<tr>
<td>Depression, adult in primary care</td>
<td>Institute for Clinical Systems Improvement (ICSI)</td>
<td>2016</td>
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<tr>
<td>Nonpharmacologic versus pharmacologic treatment of adult patients</td>
<td>American College of Physicians</td>
<td>2016</td>
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<td>with major depressive disorder</td>
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<td>Clinical guidelines for the management of adults with major</td>
<td>Canadian Network for Mood and Anxiety Treatments (CANMAT)</td>
<td>2016</td>
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<tr>
<td>depressive disorder</td>
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<tr>
<td>Management of major depressive disorder (MDD)</td>
<td>US Department of Veterans Affairs</td>
<td>2016</td>
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<tr>
<td>Practice guideline for the psychiatric evaluation of adults</td>
<td>American Psychiatric Association</td>
<td>2015</td>
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<tr>
<td>The CANMAT Task Force recommendations for mood disorders and</td>
<td>Canadian Network for Mood and Anxiety Treatment</td>
<td>2012</td>
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<td>Practice guideline for the treatment of patients with major</td>
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<td>The management of depression during pregnancy</td>
<td>American Psychiatric Association; American College of Obstetricians and</td>
<td>2009</td>
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<td>Gynecologists</td>
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<td>Guidelines for biological treatment of unipolar depressive disorders</td>
<td>World Federation of Societies of Biological Psychiatry</td>
<td>2015</td>
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<tr>
<td>part 2: maintenance treatment of major depressive disorder - update</td>
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<td>unipolar depressive disorders</td>
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<tr>
<td>Depression in adults: recognition and management</td>
<td>National Institute for Health and Care Excellence (UK)</td>
<td>2018</td>
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## International

**British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017** [191]

*Published by:* British Association for Psychopharmacology  
*Last published:* 2017

**Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines** [289]

*Published by:* British Association for Psychopharmacology  
*Last published:* 2015

**Position statement of the European Psychiatric Association (EPA) on the value of antidepressants in the treatment of unipolar depression** [290]

*Published by:* European Psychiatric Association  
*Last published:* 2012

**The European Psychiatric Association (EPA) guidance on suicide treatment and prevention** [243]

*Published by:* European Psychiatric Association  
*Last published:* 2012
### Online resources

1. [Cornell Scale For Depression in Dementia](external link)
2. [Edinburgh Postnatal Depression Scale](external link)
3. [MotherToBaby](external link)
4. [TOXNET: LactMed](external link)
Evidence scores

1. Depressive symptoms: there is medium-quality evidence that a combination of pharmacotherapy and psychotherapy improved depressive symptoms compared with either treatment alone in people with depression.
   **Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

2. Relapse: there is good-quality evidence that continuation treatment with prescription antidepressant drugs reduced the proportion of people who relapsed compared with placebo over 12 months in people who had responded to antidepressant treatment over the previous 1 to 3 months.
   **Evidence level A:** Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

3. Depressive symptoms: there is medium-quality evidence that cognitive therapy improved depressive symptoms compared with no treatment in younger and older adults with depression.
   **Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

4. Treatment success: there is good-quality evidence that interpersonal psychotherapy is effective at alleviating depression on its own or in combination with pharmacotherapy.[114]
   **Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

5. Depressive symptoms: there is medium-quality evidence that ECT improved depressive symptoms over 1 to 6 weeks' treatment compared with simulated ECT or antidepressant drugs in people with moderate to severe depression. ECT has been associated with impaired cognitive functioning immediately after treatment compared with simulated ECT.
   **Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

6. Depressive symptoms: there is poor-quality evidence that prescription antidepressant drugs (tricyclic antidepressants [including low dose tricyclic antidepressants], selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, or venlafaxine) were effective for treatment of all grades of depressive disorders compared with placebo.
   **Evidence level C:** Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.
7. Depressive symptoms: there is poor-quality evidence that high energy expenditure exercises may be more effective at improving response rates at 12 weeks.

**Evidence level C:** Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

8. Treatment success: there is poor-quality evidence that St John's wort may be more effective at treating major depression compared with placebo.

**Evidence level C:** Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.
**Key articles**

- Institute for Clinical Systems Improvement. Depression, adult in primary care. March 2016 [internet publication]. Full text


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Depression in adults

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Depression in adults

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104. Bauer M, Severus E, Köhler S, et al.; World Federation of Societies of Biological Psychiatry (WFSBF) Task Force on Treatment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders,
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patients with a chronic illness: a systematic review and meta-analysis of randomized controlled trials.


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Sep;207(3):235-42. Full text Abstract

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| 283. | Department of Veterans Affairs; Department of Defense. Management of major depressive disorder (MDD). April 2016 [internet publication]. Full text |


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