Depression in adults

The right clinical information, right where it's needed

Last updated: Nov 05, 2019
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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 examination, 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 characterised 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 characterised 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 characterised 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 characterised 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]

Aetiology

The aetiology of depression remains poorly understood. Integrative models, taking into account biological and social variables, most effectively reflect the complex aetiology. 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.

Pathophysiological 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 noradrenaline (norepinephrine) and dopamine may play a role in the fatigue and hypersomnia,[17] and impaired noradrenaline 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] [22] Structural and functional abnormalities in fronto-limbic networks were also detected in neuroimaging studies of treatment-naive patients with depression.[23] [24]

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/oranhedonia, the degree of functional impairment, and the severity of symptoms. Additionally, depressive symptoms as part of cyclothymia or bipolar disorder may also be seen.
Depression in adults

Prevention

Screening

Recommendations

The National Institute for Health and Care Excellence and The Canadian Task Force on Preventative Care both advocate screening for depression in primary care.[57]

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:[42]

‘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 postnatal women

Evidence suggests that screening pregnant and postnatal women reduces the risk of depression.[3] [4] [58] Clinicians should screen for postnatal 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 postnatal women. A score of ≥10 suggests depression.[43] [44] [45] 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 medicine 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 examination 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 postnatal period are at high risk for depression.[2] Evidence suggests that screening pregnant and postnatal women reduces the risk of depression.[3] [4] Clinicians should be vigilant in pregnancy and the weeks after delivery, and may screen for postnatal 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 non-adherence, 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...
Depression in adults

Diagnosis

retardation, irritability, and apathy. These patients may also present with severe cognitive disturbance (memory deficits) as a result of the depression.

Examination

There are no definitive findings of depression on physical examination, 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 examination 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 and the Edinburgh Depression Score for Postnatal 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.

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 recognise 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.[40] 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 work-up to exclude other causes of depression symptoms. Initial tests include thyroid function tests, metabolic panel, and full blood count. Serum vitamin B12 and folate levels, and 24-hour urinary cortisol may also be informative (and, if elevated, is suggestive of Cushing's disease).

Risk factors

Strong
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's disease and Parkinson's disease develop a depressive disorder; their carers, regardless of age, are also at increased risk.[25]

postnatal status

- Approximately 19% of postnatal 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 programmes 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.

co-existing 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.
Depression in adults

Diagnosis

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

presence of risk factors (common)

- Key risk factors include older age; recent childbirth, stress, or trauma; co-existing medical conditions (diabetes, cancer, stroke, MI, and obesity); personal or family hx of depression; certain medications (e.g., corticosteroids) and female sex.

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.[41]

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.[41]

functional impairment (common)

- According to DSM-5, symptoms cause impairment in, for example, social or occupational functions.[41]

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.[41]

libido changes (common)

- May show reduced libido.

sleep disturbance (common)

- According to DSM-5, insomnia or hypersomnia nearly every day.[41]

psychomotor problems (common)
Depression in adults

Diagnosis

• According to DSM-5, psychomotor agitation or retardation nearly every day.[41]

il energy (common)

• According to DSM-5, fatigue or loss of energy nearly every day.[41]

excessive guilt (common)

• According to DSM-5, feelings of worthlessness or excessive or inappropriate guilt nearly every day.[41]

poor concentration (common)

• According to DSM-5, diminished ability to think or concentrate nearly every day.[41]

suicidal ideation (common)

• According to DSM-5, recurrent thoughts of death, recurrent suicidal ideation without a specific plan.[41]

bipolar disorder excluded (common)

• According to DSM-5, there should be no evidence of mania or hypomania.[41]

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 pharmacological effects or side effects of prescribed medications or substances of abuse.[41]

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.[41]

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.[41]
Depression in adults

Diagnosis

1st test to order

<table>
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<th>Test</th>
<th>Result</th>
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<tr>
<td>clinical diagnosis</td>
<td>DSM-5 diagnostic criteria depending on the depressive subcategory</td>
</tr>
<tr>
<td></td>
<td>• Major depression:[1] ≥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 (&gt;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.</td>
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<tr>
<td>metabolic panel</td>
<td>normal</td>
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<td></td>
<td>• Provides baseline and may reveal metabolic disturbance.</td>
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<tr>
<td>FBC</td>
<td>normal</td>
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<td></td>
<td>• Other causes of fatigue such as anaemia should be ruled out.</td>
</tr>
<tr>
<td>thyroid function tests</td>
<td>normal</td>
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<tr>
<td></td>
<td>• An elevated serum thyroid-stimulating hormone level suggests hypothyroidism.</td>
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### Test

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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| **Patient Health Questionnaire-2 (PHQ-2)**  
- The PHQ-2  
[VIDEO: Depression (any) Screening by a Two Item PHQ-2 ]  
is derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD) tool and quickly and accurately screens for depression with only two questions:[42] ‘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?’  
- A positive response to either question warrants a thorough review of the DSM-5 criteria or an equivalent tool.  
positive result screens for depression in primary care |
| **Patient Health Questionnaire-9 (PHQ-9)**  
- The 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 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.  
positive result screens for depression in primary care |
| **Edinburgh Postnatal Depression Scale**  
- Clinicians should screen for postnatal depression using the Edinburgh Postnatal Depression Scale 4-6 weeks after delivery.  
[Edinburgh Postnatal Depression Scale] This scale is a 10-item questionnaire for postnatal 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.[43] [44] [45] Although it does not assess the severity of depression, it does assess for suicidal ideation.  
positive result screens for depression in postnatal period |
| **Geriatric Depression Scale**  
- The short form contains 15 yes/no questions.  
[VIDEO: Geriatric Depression Scale ]  
- This scale does not assess the severity of symptoms.[46] [47]  
>5 suggests depression;  
>10 strongly suggests depression |
| **Cornell Scale for Depression in Dementia**  
- This scale is a 19-item questionnaire intended for geriatric patients with dementia.  
[Cornell Scale For Depression in Dementia]  
- This scale does not assess the severity of symptoms.[48]  
>10 suggests probable depression; >18 indicates definite depression |
### Other tests to consider

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<th>Test</th>
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<tr>
<td>24-hour free cortisol</td>
<td>normal</td>
</tr>
<tr>
<td>• Elevated 24-hour urinary free cortisol level suggests Cushing’s disease.</td>
<td></td>
</tr>
<tr>
<td>vitamin B12</td>
<td>normal</td>
</tr>
<tr>
<td>• Vitamin B12 deficiency is associated with macrocytic anaemia, paraesthesia, numbness, and impaired memory.</td>
<td></td>
</tr>
<tr>
<td>folic acid</td>
<td>normal</td>
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<tr>
<td>• Patients with depression have been found to have lower levels of serum folate than normal or non-depressed psychiatric patients.[49]</td>
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## Differential diagnosis

<table>
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<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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<td><strong>Adjustment disorder with depressed mood</strong></td>
<td>• This is a subsyndromal depression with a clearly identified precipitating event. It usually does not require medicine and resolves with resolution of the acute stressor.</td>
<td>• DSM-5.</td>
</tr>
<tr>
<td><strong>Substance/medication- or medical illness-associated and other depressive disorders</strong></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, haematological, 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><strong>Bipolar disorder</strong></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><strong>Premenstrual dysphoric disorder (PMDD)</strong></td>
<td>• PMDD is characterised 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><strong>Grief reaction</strong></td>
<td>• Depressive symptoms may be transiently present in normal grief. The duration and expression of normal grief varies among racial/ethnic groups. [50] • 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>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
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<tr>
<td>Depression in adults</td>
<td>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.[51]</td>
<td></td>
</tr>
</tbody>
</table>
### Condition | Differentiating signs / symptoms | Differentiating tests
--- | --- | ---
Depression in adults | Nightmares, poor memory, and nervousness. | the CAGE questionnaire and the Alcohol Use Disorders Identification Test (AUDIT).[54]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>Eating disorders such as anorexia nervosa are more common in women and characterised 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>Medicine adverse effects</td>
<td>Patient should be asked about use of glucocorticoids, interferon, levodopa, propranolol, and oral contraceptives. The data regarding isotretinoin remain unclear.[55]</td>
<td>These effects may be temporally associated with medicine initiation.</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td>This disease is associated with progressive obesity, dermatological 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 anaemia, paraesthesia, numbness, and impaired memory.</td>
<td>Reduced serum vitamin B12 level.</td>
</tr>
<tr>
<td>Obstructive sleep apnoea (OSA)</td>
<td>Depressive symptoms are a common consequence of OSA, and can be reversed by treatment directed at the OSA.[56]</td>
<td>Sleep study.</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

**Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5)[41]**

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

Diagnosis

• Major depressive disorder
• Persistent depressive disorder (dysthymia)
• 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[41]

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)[41]

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
Depression in adults

Diagnosis

- 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[41]**

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,[60] improve workplace functioning,[61] reduce suicidality, minimise treatment adverse effects, and prevent relapse.[62] 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, organisational support, community resources, and other multidisciplinary interventions.[63] Collaborative care appears to be effective both for patients with depression alone and for those with depression and comorbid chronic physical conditions.[65] Issues yet to be resolved in the effective deployment of collaborative care models include the education of providers, reimbursement, and communication.[66] The use of internet- and mobile-based interventions have also been shown to reduce depressive symptoms.[67] [68]

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 behaviour, and health complications due to poor self-care and immobility.

Consultant referral, hospitalisation, constant observation, tranquillisation, and/or ECT may be required to keep the patient safe until definitive antidepressant therapy can take effect. The pharmacological and non-pharmacological treatment options used in these patients, once the risks have been stabilised, are discussed in the section on ‘Moderate depression’ (below).

Consultant referral is indicated and hospitalisation 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 behaviour.

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.[69] Close telephone follow-up by a trained psychiatrist may help reduce the risk of death by suicide after a previous suicide attempt.[70]

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;[71] 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 tranquillise the distress associated with this form of severe depression. Agitated patients may require
Depression in adults

**Treatment**

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,[72] and avoids complications that may arise from pharmacological intolerance and drug interactions associated with treatment for comorbid physical conditions.

- ECT is performed under general anaesthesia, 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,[73] [74] meaning that it is one of the safer procedures performed under general anaesthetic. The risk of death may be increased in patients with coronary heart disease, due to a theoretical increased risk of ischaemia 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).[75] This impairment seems to be short-lived according to objective assessment,[76] although a significant proportion of patients report persistent memory loss following ECT.[75] This potential risk must be balanced against the evidence in favour 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 able to perform their normal life tasks, they are finding it very difficult to do so.

Antidepressants are necessary in these patients,[77] [78] [79] 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.[80] [1B]Evidence Close follow-up and at minimum supportive or educational interventions during the onset of treatment can improve medication adherence.
Depression in adults

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-noradrenaline 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);
  - vortioxetine (a serotonin-reuptake inhibitor with serotonin receptor modulation properties);
  - agomelatine (a melatonin receptor agonist and 5-HT2c receptor antagonist); and
  - reboxetine (a noradrenaline-reuptake inhibitor).

- 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,[81] 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.[79] 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.[82]

- 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.[83]

- Although the net result of antidepressant response is a significant reduction in suicidal ideation,[77] [84] there is some evidence of increased suicidal behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[85] [86] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.[87] [88] 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.[89]

- Follow up patients 1 to 2 weeks after initiating therapy, then monthly for the next 12 weeks. If you prefer systematic assessment, 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
Depression in adults

Treatment

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.[90]

• If the response to first-line therapy is inadequate, consider switching to an alternative antidepressant.[91] [92] 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;[93] [94] however, be aware that early response may be, but is not necessarily, a reliable indicator of continued response.[95] [96] 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.[97]

• 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.[98] [99] [100] 2[A]Evidence Continue successful antidepressant treatment for 9 to 12 months following remission.[99] [100] 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.[101]

Psychotherapy and other non-pharmacological treatments
Depression in adults

Treatment

- Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[102][103]

- In addition to pharmacotherapeutic strategies, cognitive behavioural therapy (CBT) has shown greater efficacy than pharmacological placebo across levels of severity.[104] Treatment response to CBT is comparable with antidepressant response in some studies.[105] 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.[106][107][108] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[109] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[110]

- Therapists often use a combination of CBT[3][Evidence] and interpersonal psychotherapy (IPT)[111][4][Evidence] or problem-solving therapy (PST).[112][113] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[114] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[115] 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.[112][116]

- Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[117]

- Behavioural activation is a less cerebral, more behavioural alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomised controlled trial found it to be no less effective than CBT for adults with depression.[118]

- ECT may be an option for those who have not responded to, or cannot tolerate, antidepressants;[5][Evidence] 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[3][Evidence] or an antidepressant.[119][6][Evidence] 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.[120]

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

- Antidepressant treatment
- Psychotherapy[121][122][123]
- Supportive interventions: self-help books, yoga, relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture[124][125][126][127][128][129][130][131][132][133][134][135][136][137][138] and
- Computer-based treatment: CBT,[139][140][141][142][143][144] PST,[145][146] and stress management.[147]

Antidepressant treatment
Depression in adults

Treatment

• An antidepressant may be preferable in some patients as it may offer a more rapid response than non-pharmacological 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.[148] There is essentially no consistent evidence that any of the traditional antidepressants are superior to any other.[149]

• 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.[83]

• 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.[99] [100] 2[A]Evidence 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.[150] Mild depression treated with psychotherapy may be less likely to progress to severe depression.[151] Psychoeducation alone can achieve remission for some patients.[152]

• Therapists often use a combination of CBT3[B]Evidence and IPT[111] 4[B]Evidence or PST.[112] [113] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[114] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[115] 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.[153]

Supportive interventions

• Self-help books are popular and bibliotherapy has demonstrated better efficacy than no treatment at all.[154]

• Yoga may have a beneficial effect on depressive disorders, but there are significant variations in interventions, reporting, and feasibility.[155] [156] 7[C]Evidence

• Other supportive interventions include relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture.[124] [125] [126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [136] [137] [138] In non-remitted patients, higher remission rates were observed in a higher-dose exercise group plus continuation of SSRI treatment compared with low-dose exercise plus SSRIs.[157] Conversely, cessation of exercise may worsen depressive symptoms.[158] [159]

• St John’s wort is a herb that is considered to be effective for the treatment of mild to moderate depression.[160] [161] 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.[162][163] 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.[162][163]

Computer-based treatment

- Evidence supports the efficacy of computer-based CBT,[139][140][141][142][143][144] PST,[145][146] and stress management.[147] 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.[164] 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.[165]

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, adverse 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 centered on individual patients may be feasible, but have not often been used.[166]

**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 demoralised attitude) can reflect behavioural adaptations to depression, rather than the disease itself. In such cases, symptoms may best be corrected through behavioural 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.[167][168][169][170] There is some evidence that failure on one or several antidepressants does not preclude later success.[171][164] 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.[172]
Depression in adults

Treatment

• 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 favour 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.[173] The washout period depends on the half-life off 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.[174] 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 rehospitalisation after severe depression, but is also more effective on its own than when combined with antidepressants.[175] The addition of an atypical antipsychotic to an antidepressant has been historically controversial:[176] [177] however, augmentation with some agents is becoming more common practice and may improve outcomes.[178] [179] Second-generation antipsychotic medications used in combination with antidepressants demonstrate efficacy and their use is becoming widespread.[180] 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.[178] Aripiprazole, which the US 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.[179] Brexiprazole, a novel serotonin-dopamine activity modulator, is approved by the FDA as an adjunctive treatment for major depressive disorder,[181] although the evidence for its efficacy derives from a relatively small number of studies.[182] Weight gain and akathisia are among the most commonly reported adverse effects, and small effects on glucose and lipids have also been noted.[183] While some benefit has been demonstrated in meta-analysis of clinical trial data, it is unclear whether benefits outweigh risks in people without psychosis.[176] Other augmentation strategies used by specialists include thyroid hormone, modafinil, ketamine, and pindolol.[184] [185] [186]

Non-pharmacological approaches

• Check and ensure that the patient has started psychotherapy if multiple pharmacological 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 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.[100] 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.[187] [188] Unfortunately, there is little controlled trial evidence.[189] Consistent data to support fully-informed decision-making are lacking.[190] [191] [192] [193] [194] [195] [196]

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.[197] 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.[198] 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.[199]

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 an antenatal psychiatric disorder and no antidepressant use.[200] [201] [202]

It is fairly clear that women who stop their antidepressant are more likely to have a relapse of depression during their pregnancy.[203] 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 behaviour in later childhood and adolescence.[204]

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,
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. [UK Teratology Information Service]

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.[205] [206] 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.[207] [188] [189] Treat mild depression in pregnancy as you would any other, perhaps with a slightly higher threshold for using medication than you would with a non-pregnant patient. The risk/benefit balance may tip in favour of non-pharmacological 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.[208]

There is evidence to support the use of counselling interventions, such as CBT and interpersonal psychotherapy, to prevent depression in pregnant and postnatal 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.[209]

**Postnatal depression**

Screen women with risk factors for postnatal depression to prevent or immediately treat postnatal depression. There is evidence from combined studies that CBT may be effective for both prevention and treatment of postnatal depressive symptoms.[210] Longer-term therapy may further enhance psychotherapeutic benefits to mothers and their offspring. Pharmacotherapy requires careful consideration. Many breastfeeding 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 breastfeeding. 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 behaviour.

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

For more detailed information, please see our separate topic on Postnatal 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.[211]
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,[212] 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.[213] Antidepressant use in depressed patients who are on opioid agonist therapy is not well supported.[214] 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.[215] Evidence is also low quality, but more favourable, for antidepressants in patients with depression and HIV infection.[216] Support for antidepressants for depression comorbid with cancer is mixed.[217] [218]

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.
### Treatment

<table>
<thead>
<tr>
<th>Depression in adults</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>(summary)</td>
</tr>
<tr>
<td><strong>severe depression, non-pregnant:</strong> psychotic, suicidal, severe psychomotor retardation impeding activities of daily living, catatonia, or severe agitation</td>
<td></td>
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<tr>
<td>1st psychiatric referral ± hospitalisation + antidepressant</td>
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<tr>
<td>adjunct immediate symptom management with benzodiazepine ± antipsychotic</td>
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</tr>
<tr>
<td>1st psychiatric referral ± hospitalisation + electroconvulsive therapy (ECT)</td>
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<tr>
<td>plus antidepressant</td>
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<tr>
<td>adjunct immediate symptom management with benzodiazepine ± antipsychotic</td>
<td></td>
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<tr>
<td>2nd switch to alternative antidepressant</td>
<td></td>
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<tr>
<td><strong>moderate depression, non-pregnant:</strong> severe symptoms, significant impairment but no psychotic symptoms, no suicidal ideation, and no severe psychomotor retardation or agitation</td>
<td></td>
</tr>
<tr>
<td>1st antidepressant</td>
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<td>adjunct psychotherapy or other non-pharmacological treatment</td>
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<tr>
<td>adjunct immediate symptom management with benzodiazepine ± antipsychotic</td>
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<tr>
<td><strong>mild depression, non-pregnant:</strong> low to moderate severity symptoms, partial impairment, no psychotic symptoms, no suicidal ideation, and no psychomotor retardation or agitation</td>
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<tr>
<td>1st antidepressant</td>
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<td>1st psychotherapy</td>
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<td>1st computer-based interventions</td>
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<tr>
<td>2nd switch to alternative antidepressant#</td>
<td></td>
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<tr>
<td>3rd St John’s wort</td>
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</tr>
</tbody>
</table>
### Acute

| treatment-resistant/refractory depression | 1st | reassess and switch to alternative antidepressant or try combination therapy |
|                                          | plus | consider augmentation therapy |
|                                          | plus | psychotherapy or other non-pharmacological treatment |
| 2nd                                      | monoamine oxidase inhibitor (MAOI) |
| 2nd                                      | plus | psychotherapy or other non-pharmacological treatment |
| 3rd                                      | electroconvulsive therapy (ECT) |

#### pregnant

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

#### Ongoing

<table>
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<tr>
<td>adjunct</td>
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</tbody>
</table>

#### recurrent episode

<table>
<thead>
<tr>
<th>1st</th>
<th>repeat of remission-inducing regimen or long-term therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>plus</td>
<td>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 Treatment

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

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

### Primary options

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

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

- **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.

- **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

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

- **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
### Acute

- **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:** 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

**Secondary options**
Depression in adults

Treatment

**Acute**

- **agomelatine**: 25 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day

**OR**

- **reboxetine**: 4 mg orally twice daily initially, increase gradually according to response, maximum 12 mg/day

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

- 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 behaviour. If the patient is unwilling to be hospitalised, 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.

- 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.

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

Acute

» No consistent differences in safety or efficacy have been demonstrated between antidepressants,[81] 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.[79] 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.[82]

» 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.[83]

» Although the net result of antidepressant response is a significant reduction in suicidal ideation,[77] [84] there is some evidence of increased suicidal behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[85] [86] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.[87] [88] 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.[89]

» 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.[219] 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
Depression in adults

Treatment

**Acute**

- support routinely increasing the dose beyond the established dose range.[90]

» Follow up patients 1 to 2 weeks after initiating therapy, then monthly for the next 12 weeks. If you prefer systematic assessment, 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.

» Continue successful antidepressant treatment for 9 to 12 months following remission.[99][100] 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
## Acute

| |  
|---|---|
|  | » 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. Consult local guidance for other examples and preferred options.

Emergency treatment of mood disorder symptoms aims to stabilise 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 behaviour. 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.[71]

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...
Depression in adults

Treatment

**Acute**

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 tranquilising agents.

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

» 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 behaviour. If the patient is unwilling to be hospitalised, 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.[220] 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,[72] and avoids the complications that may arise from pharmacological intolerance and drug interactions associated with treatment for comorbid physical conditions.

» ECT is performed under general anaesthesia, 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,[73] [74] meaning that it is one of the safer procedures performed under general
## Acute

anaesthetic. The risk of death may be increased in patients with coronary heart disease, due to a theoretical increased risk of ischaemia 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). This impairment seems to be short-lived according to objective assessment, although a significant proportion of patients report persistent memory loss following ECT. This potential risk must be balanced against the evidence in favour of its efficacy, especially in patients with severe depression.

### plus antidepressant

Treatment recommended for ALL patients in selected patient group

### Primary options

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

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

- **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.

- **paroxetin**: 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

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

| TREATMENT | 
| --- | --- |
| 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 | 
| 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**: 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 |
Depression in adults

Treatment

**Acute**

» **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

**Secondary options**

» **agomelatine**: 25 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day

OR

» **reboxetine**: 4 mg orally twice daily initially, increase gradually according to response, maximum 12 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-noradrenaline reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone, vortioxetine, reboxetine, and agomelatine).

» No consistent differences in safety or efficacy have been demonstrated between antidepressants,[81] 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.[79] 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.[82]

» 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...
Depression in adults

TREATMENT

Acute

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.[83]

» Although the net result of antidepressant response is a significant reduction in suicidal ideation,[77] [84] there is some evidence of increased suicidal behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[85] [86] Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm.[87] [88] 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.[89]

» 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.[219] In a minority of patients, pharmacogenomical 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.[90]

» Follow up patients 1-2 weeks after initiating therapy, then monthly for the next 12 weeks. If systematic assessment 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 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;[99] [100] Evidence however, some physicians

[83] [84] [85] [86] [87] [88] [89] [90] [99] [100]
### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>adjunct</th>
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</thead>
<tbody>
<tr>
<td>immediate symptom management with benzodiazepine ± antipsychotic</td>
<td></td>
</tr>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

**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. Consult local guidance for other examples and preferred options.

- Emergency treatment of mood disorder symptoms aims to stabilise 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...
Depression in adults

### Treatment

**Acute**

- Behaviour. 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.

- 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 tranquilising agents.

<table>
<thead>
<tr>
<th>2nd switch to alternative antidepressant</th>
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- If the response to first-line therapy is inadequate, consider switching to an alternative antidepressant.\[91\] [92] 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;\[93\] [94] however, early response may be, but is not necessarily, a reliable indicator of continued response.\[95\] [96] 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.\[97\]

- Consider a change in drug class; if a patient was on a selective serotonin-reuptake inhibitor, then try a serotonin noradrenaline-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,
Depression in adults

Treatment

**Acute**

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, 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;[99] [100] 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.

<table>
<thead>
<tr>
<th>moderate depression, non-pregnant: severe symptoms, significant impairment but no psychotic symptoms, no suicidal ideation, and</th>
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### Acute

**no severe psychomotor retardation or agitation**

<table>
<thead>
<tr>
<th>1st antidepressant</th>
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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>
<td><strong>OR</strong></td>
</tr>
<tr>
<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>
<td><strong>OR</strong></td>
</tr>
<tr>
<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>
<td><strong>OR</strong></td>
</tr>
</tbody>
</table>
### Acute

**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**: 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

### Secondary options

**OR**

- **agomelatine**: 25 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day
Treatment

Acute

- **reboxetine**: 4 mg orally twice daily initially, increase gradually according to response, maximum 12 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-noradrenaline reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone, vortioxetine, reboxetine, and agomelatine).

- No consistent differences in safety or efficacy have been demonstrated between antidepressants,[81] 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.[79] 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.[82]

- 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 pharmacogenomical analysis is not yet recommended for widespread use.[83]

- Although the net result of antidepressant response is a significant reduction in suicidal ideation,[77][84] there is some evidence of increased suicidal behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting...
### Acute

<table>
<thead>
<tr>
<th>adjunct psychotherapy or other non-pharmacological treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td>» Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.</td>
</tr>
<tr>
<td>» In addition to pharmacotherapeutic strategies, cognitive behavioural therapy (CBT) has shown greater efficacy than pharmacological</td>
</tr>
</tbody>
</table>
### Acute

placebo across levels of severity.\[104\]

Treatment response to CBT is comparable with antidepressant response in some studies.\[105\]

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.\[106\] \[107\] \[108\] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.\[109\]

Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.\[110\]

- Therapists often use a combination of CBT\[3B\]Evidence and interpersonal psychotherapy (IPT)\[111\] \[4B\]Evidence or problem-solving therapy (PST).\[112\] \[113\]

IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.\[114\] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.\[115\]

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.\[112\] \[116\]

- Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.\[117\]

- Behavioural activation is a less cerebral, more behavioural alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomised controlled trial found it to be no less effective than CBT for adults with depression.\[118\]

**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

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Depression in adults

Treatment

### Acute

OR

- **quetiapine**: 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. Consult local guidance for other examples and preferred options.

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.

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 tranquillising agents.

### 2nd switch to alternative antidepressant

- If the response to first-line therapy is inadequate, consider switching to an alternative antidepressant.[91] [92] 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;[93] [94] however, early response may be, but is not necessarily, a reliable indicator of continued response.[95] [96] 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.[97]

- Consider a change in drug class; if a patient was on a selective serotonin-reuptake inhibitor, then try a serotonin noradrenaline-reuptake inhibitor. If treatment was not tolerated due to
Depression in adults

TREATMENT

Acute

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;[99] [100] 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.

adjunct psychotherapy or other non-pharmacological treatment

Treatment recommended for SOME patients in selected patient group
Acute

» Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[102] [103]

» In addition to pharmacotherapeutic strategies, cognitive behavioural therapy (CBT) has shown greater efficacy than pharmacological placebo across levels of severity.[104] Treatment response to CBT is comparable with antidepressant response in some studies.[105] 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.[106] [107] [108] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[109] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[110]

» Therapists often use a combination of CBT[3B]Evidence and interpersonal psychotherapy (IPT)[111] or problem-solving therapy (PST).[112] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[114] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[115] 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.[112] [116]

» Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[117]

» Behavioural activation is a less cerebral, more behavioural alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomised controlled trial found it to be no less effective than CBT for adults with depression.[118]

| mild depression, non-pregnant: |
| low to moderate severity symptoms, |
| partial impairment, no psychotic symptoms, no suicidal ideation, and no psychomotor retardation or agitation |

| 1st antidepressant |
### Acute

#### 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

OR
<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
</tr>
<tr>
<td>» <strong>levomilnacipran</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>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» <strong>venlafaxine</strong>: 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>OR</td>
</tr>
<tr>
<td>» <strong>bupropion</strong>: 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>
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<td>OR</td>
</tr>
<tr>
<td>» <strong>mirtazapine</strong>: 15 mg orally once daily initially, increase gradually according to response, maximum 45 mg/day</td>
</tr>
<tr>
<td>OR</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>
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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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<tr>
<td><strong>Secondary options</strong></td>
</tr>
<tr>
<td>» <strong>agomelatine</strong>: 25 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day</td>
</tr>
</tbody>
</table>
### Treatment

#### Acute

- **reboxetine**: 4 mg orally twice daily initially, increase gradually according to response, maximum 12 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 behavioural therapy [Evidence] or an antidepressant. 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-noradrenaline reuptake inhibitors (SNRIs) (e.g., desvenlafaxine, duloxetine, levomilnacipran, venlafaxine), and other atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone, vortioxetine, reboxetine, and agomelatine).

- 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 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.

- Although the net result of antidepressant response is a significant reduction in suicidal ideation, there is some evidence of increased suicidal behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses. Some evidence suggests that teenagers and young adults are especially likely to experience an increase in thoughts of suicide and self-harm. 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...
Acute

weeks 3-6 of treatment (but not in weeks 1-2), which is later than has been suggested by other studies.[89]

» 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.[219] 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.[90]

» Follow up patients 1-2 weeks after initiating therapy, then monthly for the next 12 weeks. If you prefer systematic assessment, 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;[99] [100] 2[A]Evidence 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.[150] Mild depression treated with psychotherapy may be less likely to progress to severe depression.[151] Psychoeducation alone can achieve remission for some patients.[152]

» Therapists often use a combination of cognitive behavioural therapy (CBT)3[B]Evidence and interpersonal psychotherapy (IPT)4[B]Evidence or problem-solving therapy.[112] [113] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[114] IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.[115] Frequency for both CBT and IPT is determined by the healthcare provider.
Depression in adults

Treatment

Acute

The time to response is approximately 12 weeks. Time-limited psychodynamic therapy has also gained empirical support as a treatment for major depression.[153]

1st supportive interventions

» Self-help books are popular and bibliotherapy has demonstrated better efficacy than no treatment at all.[154] Cognitive bibliotherapy has shown outcomes similar to those of psychotherapy.[221] There are no data on bibliotherapy alone. Two recommended texts are 'Feeling good: the new mood therapy' by David D. Burns, and 'Managing anxiety and depression: a self-help guide' by Nicholas Holdsworth and Roger Paxton.[222] [223] [224] The former is based on the cognitive behavioural therapy approach. One meta-analysis found a large improvement at 4 weeks, but the participants appeared to have a very high educational level.[225]

» Yoga interventions may have a beneficial effect on depressive disorders, but there are significant variations in interventions, reporting, and feasibility.[155] [156] 7[C]Evidence

» Other supportive interventions include relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture.[124] [125] [126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [136] [137] [138] In non-remitted patients, higher remission rates were observed in a higher-dose exercise group plus continuation of serotonin noradrenaline-reuptake inhibitor treatment compared with low-dose exercise plus selective serotonin-reuptake inhibitors.[157] Conversely, cessation of exercise may worsen depressive symptoms.[158] [159]

1st computer-based interventions

» Evidence supports the efficacy of computer-based cognitive behavioural therapy,[139] [140] [141] [142] [143] [144] problem-solving therapy,[145] [146] and stress management.[147] 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.[91] [92] 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

Treatment

Acute

weeks of treatment; however, early response may be, but is not necessarily, a reliable indicator of continued response. 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.

Consider a change in drug class; if a patient was on a selective serotonin-reuptake inhibitor, then try a serotonin noradrenaline-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.

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
## Acute

then ‘start low and go slow’ until safety can be ascertained.

- Continue successful antidepressant treatment for 9-12 months following remission.\[99\] [100] 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.\[160\] [161] 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.\[226\] [227]

- 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>
<th>1st</th>
<th>reassess and switch to alternative antidepressant or try combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <strong>citalopram</strong>: 20 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day</td>
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<td></td>
<td><strong>OR</strong></td>
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<tr>
<td></td>
<td></td>
<td>- <strong>escitalopram</strong>: 10 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day</td>
</tr>
</tbody>
</table>
Depression in adults

Acute

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

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,
### Treatment

#### Acute

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute increase gradually according to response, maximum 225 mg/day</strong></td>
<td></td>
</tr>
<tr>
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<tr>
<td><strong>bupropion</strong>: 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>
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<td><strong>mirtazapine</strong>: 15 mg orally once daily initially, increase gradually according to response, maximum 45 mg/day</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><strong>OR</strong></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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<td><strong>OR</strong></td>
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<td><strong>doxepin</strong>: 25-75 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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### Treatment

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<tbody>
<tr>
<td>OR</td>
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<td>» <strong>imipramine</strong>: 25-75 mg orally once daily at bedtime initially, increase gradually according to response, maximum 150-300 mg/day (may give in divided doses)</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» <strong>nortriptyline</strong>: 25-50 mg orally once daily at bedtime initially, increase gradually according to response, maximum 150 mg/day (may give in divided doses)</td>
</tr>
</tbody>
</table>

**Secondary options**

| OR                          |
| » **agomelatine**: 25 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day |
| OR                          |
| » **reboxetine**: 4 mg orally twice daily initially, increase gradually according to response, maximum 12 mg/day |

» 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. 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.

» 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 demoralised attitude) can reflect behavioural adaptations to depression, rather than the disease itself. In such cases, symptoms may best be corrected through behavioural 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
### Acute

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 noradrenaline-reuptake inhibitors (SNRI), or an atypical agent (e.g., bupropion, mirtazapine, vilazodone, vortioxetine, reboxetine, and agomelatine). 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.[167] [168] [169] [170] There is some evidence that failure on one or several antidepressants does not preclude later success.[171] [164] 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.[172]

» 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 favour 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,
Depression in adults

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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;[99] [100]

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
TREATMENT

Acute

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,[176] [177] however, augmentation with some agents is becoming more common practice and may improve outcomes.[178] [179] Second-generation antipsychotic medications used in combination with antidepressants demonstrate efficacy and their use is becoming widespread.[180] Some studies show that combinations of antidepressants with other classes of medication are better than just a combination of different antidepressants alone.[174]

» 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 rehospitalisation after severe depression, but is also more effective on its own than when combined with antidepressants.[175]

» 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.[178] Aripiprazole, which the US 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.[179]

» Brexpiprazole, a novel serotonin-dopamine activity modulator, is approved by the FDA as an adjunctive treatment for major depressive disorder,[181] although the evidence for its
**Acute**

<table>
<thead>
<tr>
<th>depression in adults</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Efficacy derives from a relatively small number of studies.</td>
<td>[182] Weight gain and akathisia are among the most commonly reported adverse effects, and small effects on glucose and lipids have also been noted.</td>
</tr>
<tr>
<td>Other augmentation strategies used by specialists include thyroid hormone, modafinil, ketamine, and pindolol.</td>
<td>[184] [185] [186]</td>
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<tr>
<td>plus psychotherapy or other non-pharmacological treatment</td>
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<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
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</tr>
<tr>
<td>» Check and ensure that the patient has started psychotherapy if multiple pharmacological agents have been unsuccessful.</td>
<td></td>
</tr>
<tr>
<td>» Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.</td>
<td>[102] [103]</td>
</tr>
<tr>
<td>» In addition to pharmacotherapeutic strategies, cognitive behavioural therapy (CBT) has shown greater efficacy than pharmacological placebo across levels of severity.</td>
<td>[104]</td>
</tr>
<tr>
<td>Treatment response to CBT is comparable with antidepressant response in some studies.</td>
<td>[105]</td>
</tr>
<tr>
<td>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.</td>
<td>[106] [107] [108]</td>
</tr>
<tr>
<td>In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.</td>
<td>[109]</td>
</tr>
<tr>
<td>Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.</td>
<td>[110]</td>
</tr>
<tr>
<td>» Therapists often use a combination of CBT and interpersonal psychotherapy (IPT) or problem-solving therapy (PST).</td>
<td>[111] [112] [113]</td>
</tr>
<tr>
<td>IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.</td>
<td>[114]</td>
</tr>
<tr>
<td>IPT is useful only if the patient has the capacity for psychological insight and is committed to longer-term therapy.</td>
<td>[115]</td>
</tr>
<tr>
<td>Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. PST focuses on...</td>
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### Acute

<table>
<thead>
<tr>
<th>2nd</th>
<th>Monoamine oxidase inhibitor (MAOI)</th>
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<tr>
<td></td>
<td><strong>Primary options</strong></td>
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<tr>
<td></td>
<td>» isocarboxazid: 10 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day given in 2-4 divided doses</td>
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<td>OR</td>
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<td></td>
<td>» 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</td>
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<td>OR</td>
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<td></td>
<td>» selegiline transdermal: 6 mg/24 hours patch once daily initially, increase gradually according to response, maximum 12 mg/24 hours</td>
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<td>OR</td>
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<tr>
<td></td>
<td>» tranylcypromine: 30 mg/day orally initially given in 2-3 divided doses, increase gradually according to response, maximum 60 mg/day</td>
</tr>
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</table>

- 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, adrenaline, 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
Depression in adults

Treatment

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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;[99] [100]

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 psychotherapy or other non-pharmacological treatment

Treatment recommended for ALL patients in selected patient group

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

» Psychotherapy in various forms has been shown to be both effective and cost-effective in reducing depressive symptoms.[102] [103]
In addition to pharmacotherapeutic strategies, cognitive behavioural therapy (CBT) has shown greater efficacy than pharmacological placebo across levels of severity.[104] Treatment response to CBT is comparable with antidepressant response in some studies.[105] 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.[106] [107] [108] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[109] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[110]

Therapists often use a combination of CBT and interpersonal psychotherapy (IPT) or problem-solving therapy (PST).[111] [112] [113] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[114] 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.[112] [116]

Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[117]

Behavioural activation is a less cerebral, more behavioural alternative to CBT. It actively promotes a return to functioning and has the advantage of not requiring doctoral-level therapists to administer it. One randomised controlled trial found it to be no less effective than CBT for adults with depression.[118]

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 anaesthesia, 2 or 3 times a week for a total of 6-12
### Acute

Improvement is usually noted after several treatments.\[220\]

- The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments,\[73\] \[74\] meaning that it is one of the safer procedures performed under general anaesthetic. The risk of death may be increased in patients with coronary heart disease, due to a theoretical increased risk of ischaemia during the induced seizure. Short-term cognitive adverse effects (e.g., amnesia) are common,\[75\] and a significant proportion of patients report persistent memory loss following ECT.

### pregnant

<table>
<thead>
<tr>
<th>1st</th>
<th>antidepressant or electroconvulsive therapy (ECT)</th>
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<tbody>
<tr>
<td>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.[205] [206]</td>
<td></td>
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<tr>
<td>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.[207] [188] [189]</td>
<td></td>
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<tr>
<td>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 non-pregnant patient. There is little consistent controlled evidence that antidepressants should be contraindicated during pregnancy, but the risk/benefit balance may tip in favour of non-pharmacological therapies, particularly because many patients may have reservations about using medication when pregnant.</td>
<td></td>
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<tr>
<td>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.[199] 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 on bestpractice.bmj.com.</td>
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Depression in adults

Treatment

### Acute

<table>
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<tr>
<th>plus</th>
<th>psychotherapy</th>
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<tr>
<td></td>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td></td>
<td>Cognitive behavioural 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. [208]</td>
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[UK Teratology Information Service]
**Depression in adults**

**Treatment**

<table>
<thead>
<tr>
<th>Ongoing</th>
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<td>treatment responsive</td>
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1st **maintenance antidepressant therapy**

» Continue the antidepressant regimen that led to remission for 9-12 months following remission;[99] [100] 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.

**adjunct psychotherapy**

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.[102] [103]

» Continued psychotherapy with antidepressant management is an effective option when continued through both acute and ongoing phases of treatment.[120] Staged treatment trials suggest that cognitive behavioural 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.[106] [107] [108]

» In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[109] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[110]

» Therapists often use a combination of CBT3[B]Evidence and interpersonal psychotherapy (IPT)[111] 4[B]Evidence or problem-solving therapy (PST).[112] [113] IPT may improve interpersonal functioning, whereas CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[114] 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.[112] [116]

» Bibliotherapy, a program of self-help by reading, may have long-term benefits for some patients.[117]

» Behavioural activation is a less cerebral, more behavioural alternative to CBT. It actively promotes a return to functioning and has
Ongoing

the advantage of not requiring doctoral-level therapists to administer it. One randomised controlled trial found it to be no less effective than CBT for adults with depression.[118]

» Mild depression treated with psychotherapy may be less likely to progress to severe depression.[151]

recurrent episode

1st repeat of remission-inducing regimen or long-term therapy

» 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.

» 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.

plus psychotherapy

Treatment recommended for ALL patients in selected patient group

» 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][229] 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 psychedelic drug, has received breakthrough therapy designation from the US Food and Drug Administration (FDA) for treatment-resistant depression.[231]

Esketamine nasal spray

In March 2019 the US 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 sedation, difficulty with attention, judgement and thinking (dissociation), suicidal thoughts and behaviours, 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.[232] 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.[233] 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.[234] The most common side effects were dissociation, dizziness, nausea, sedation, vertigo, decreased feeling or sensitivity (hypoesthesia), anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.[235] 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 pre-frontal cortex,[236] and guidelines for best practice are being developed.[237] 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 depolarise cortical neurons, generating action potentials and leading to biological effects.[236] The absence of psychosis and younger age may predict success.[236] Review of literature has found inconsistent evidence of a benefit in depression.[238][239][240][241] and some evidence of a synergistic effect with concurrent antidepressant treatment.[242] 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.[243] 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.[244] Work is ongoing to establish whether variation in treatment parameters might affect outcomes.[245] Other evidence suggests that TMS is no different from sham TMS treatment in patients with depression.[246] Large-scale studies are needed.[247]

Non-steroidal anti-inflammatory drugs (NSAIDs)

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.[248]
Vagus nerve stimulation (VNS)
VNS entails stimulation of the left cervical vagus nerve, using a commercial device termed the VNS Therapy System.[249] A generator, about the size of a pocket watch, is implanted subcutaneously into the left chest wall and is connected to bipolar electrodes attached to the left vagus nerve.[250] The generator is programmed to deliver mild electric pulses in continuous cycles, typically with 30 seconds of stimulation followed by 5 minutes off.[250] VNS has been approved in Canada, Europe, and the US for the adjunctive long-term treatment of chronic depression for patients aged 18 years and older, who are experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments.[251] [252] One meta-analysis found no conclusive evidence for the efficacy of VNS in the treatment of depression.[253]

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.[254] Results are limited by small sample size and insufficient randomised control data.[255] [256]

Transcranial direct current stimulation (tDCS)
Similar to TMS in the localisation of treatment and tolerability but uses current rather than magnetic field. While the effect size was similar to that of TMS in some studies,[257] results from other trials have been mixed.[258] 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.[259]

Methylphenidate and thyroid hormone
The benefits of methylphenidate and thyroid hormone as single or co-therapy remain controversial.[260] [261] [262] [263] [264]

Nutraceuticals
Adjunctive use of pharmaceutical-grade nutrients, such as S-adenosylmethionine (SAMe), acetylcysteine, 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.[265] [266] [267] [268] 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 non-depressed psychiatric patients.[49] Supplementation with folic acid may be beneficial in depressed patients with folate deficiency. 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.[49] [269] One 2×2 factorial randomised clinical trial of multiniutrients (omega-3 fatty acids, selenium, folic acid, and vitamin D3 plus calcium), therapy (group or individual), or their combination, given to overweight patients with sub-syndromal depressive symptoms showed that multiniutrients did not reduce episodes of major depressive disorder over the 1 year.[270]

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,[271] however, the data are too limited to make it a standard treatment for depression.[272] 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.[273] [274] In a multicentre trial, intravenous ketamine demonstrated sustained efficacy over a 2-week period.[275] 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 neurological effects. The most common somatic effects were headache, dizziness, dissociation, elevated blood pressure, and blurred vision.[276] However, its safety and
efficacy for long-term use remain unknown.[277] [278] Repeated use of ketamine in other patient groups has been linked to urological and liver toxicity, cognitive deficits, and dependency.[276]

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-metabolising enzymes in an individual.[279] 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 metaboliser who excretes the drug before it can adequately perfuse the brain), or low doses (for a slow metaboliser who may find recommended drug doses to have intolerable side effects). These tests may improve outcome,[280] but have not proven to be cost effective in practice. Pharmacogenomic analysis is not yet recommended for routine use.[83]
Depression in adults

Follow up

Recommendations

Monitoring

Initial

- Non-adherence 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 hospitalisation. One half or more of patients receiving antidepressants fail to take them at an adequate dose for an adequate duration.[290] [291] 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 medicine 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, examination, and laboratory studies can prove vital in monitoring for, and preventing adverse effects from, treatment.[292] 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,[293] as is text messaging.[294]
- 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.[295]

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.[99] [100] [2A]Evidence Educate patients and their families to self-assess for symptoms and risk for recurrent episodes, and continue to re-screen patients at regularly scheduled appointments.
- Use the Patient Health Questionnaire-9 (PHQ-9) to assess changes in symptom severity objectively. 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. Programmes have been shown in multiple practice settings to improve care. Key elements of the care pathways can include co-ordination 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.[63] [293] [296] [297] [298] [299] [294] There may be an increasing role for self-help and self-guided interventions such as behavioural activation strategies and internet-based therapy,[300] [301] 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.[302]

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. Medicines and psychotherapy are the most common treatments. There are many different types of antidepressant medicines. These medicines may take several weeks before they become effective and should be taken for many months to prevent symptoms from coming back. Medicines 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 medicines.

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>
</tr>
</thead>
<tbody>
<tr>
<td>sexual adverse effects of selective serotonin-reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs)#</td>
<td>short term</td>
<td>medium</td>
</tr>
</tbody>
</table>

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.[281] [282] The addition of bupropion or trazodone to SSRI therapy may also be helpful.[283]

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>risk of self-injurious behaviour</td>
<td>short term</td>
<td>medium</td>
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</table>

Children, adolescents, and young adults may experience a transient increase in risk for self-injury, most severe with rapid escalation in dosing.[86]

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>undesired weight gain from antidepressants</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

Weight gain is most common with mirtazapine but can also be seen with SSRIs, venlafaxine, and tricyclic antidepressants. Patient may be switched to bupropion.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>agitation or excessive activation from antidepressants</td>
<td>short term</td>
<td>low</td>
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</table>

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.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>unmasking mania</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

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.[284] Depressed patients with undiagnosed bipolar affective disorder may convert to frank mania if they receive antidepressant medicine. 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 judgement) 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 stabiliser, preferably under psychiatric supervision. Early initiation of mood-stabiliser drug therapy in bipolar disorder is important.[285]

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>mania due to antidepressant withdrawal</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

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.[286]

The syndrome may be self-limiting, may abate with the re-institution of the antidepressant, or may require anti-manic treatment. Mood stabilisers do not necessarily protect against the syndrome.[287]

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>antidepressant discontinuation syndrome</td>
<td>short term</td>
<td>low</td>
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</table>
Depression in adults

**Complications**

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>variable</td>
</tr>
</tbody>
</table>

The use of SSRIs may be associated with an increased risk of suicidal behaviour in patients under 25 years old and reduced risk in adults over 25 years old.[62] [288] [289]

**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.[99] [100] [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.[100]

Depression recurs in about one third of patients within 1 year of discontinuing treatment and in more than 50% of patients during their lifetime.[11] Evidence that antidepressants can prevent relapse is unclear.[100] [111] After 15 years, 87% will experience a recurrence. For patients with 3 recurrent depressive episodes, many experts advocate long-term maintenance therapy.
## Diagnostic guidelines

### North America

<table>
<thead>
<tr>
<th>Title</th>
<th>Published by</th>
<th>Last published</th>
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<tbody>
<tr>
<td><strong>Perinatal depression: preventive interventions</strong></td>
<td>US Preventive Services Task Force</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Screening for perinatal depression</strong></td>
<td>American College of Obstetricians and Gynecologists</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Screening for depression in adults</strong></td>
<td>US Preventive Services Task Force</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Practice guideline for the psychiatric evaluation of adults</strong></td>
<td>American Psychiatric Association</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Recommendations on screening for depression in adults (for clinicians and policy makers)</strong></td>
<td>Canadian Task Force on Preventive Health Care</td>
<td>2013</td>
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## Treatment guidelines

### Europe

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<tr>
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<tbody>
<tr>
<td>Depression in adults: recognition and management</td>
<td>National Institute for Health and Care Excellence</td>
<td>2018</td>
</tr>
<tr>
<td>British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017</td>
<td>British Association for Psychopharmacology</td>
<td>2017</td>
</tr>
<tr>
<td>Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines</td>
<td>British Association for Psychopharmacology</td>
<td>2015</td>
</tr>
<tr>
<td>The European Psychiatric Association (EPA) guidance on suicide treatment and prevention</td>
<td>European Psychiatric Association</td>
<td>2012</td>
</tr>
<tr>
<td>Position statement of the European Psychiatric Association (EPA) on the value of antidepressants in the treatment of unipolar depression</td>
<td>European Psychiatric Association</td>
<td>2012</td>
</tr>
<tr>
<td>Vagus nerve stimulation for treatment-resistant depression</td>
<td>National Institute for Health and Care Excellence</td>
<td>2009</td>
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### International

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<tr>
<td>Guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders</td>
<td>World Federation of Societies of Biological Psychiatry</td>
<td>2013</td>
</tr>
</tbody>
</table>
### North America

**Depression, adult in primary care**

*Published by:* Institute for Clinical Systems Improvement (ICSI)  
*Last published:* 2016

**Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder**

*Published by:* American College of Physicians  
*Last published:* 2016

**Clinical guidelines for the management of adults with major depressive disorder**

*Published by:* Canadian Network for Mood and Anxiety Treatments (CANMAT)  
*Last published:* 2016

**Management of major depressive disorder (MDD)**

*Published by:* US Department of Veterans Affairs  
*Last published:* 2016

**Practice guideline for the psychiatric evaluation of adults**

*Published by:* American Psychiatric Association  
*Last published:* 2015

**The CANMAT Task Force recommendations for mood disorders and co-morbid conditions**

*Published by:* Canadian Network for Mood and Anxiety Treatment  
*Last published:* 2012

**Practice guideline for the treatment of patients with major depressive disorder**

*Published by:* American Psychiatric Association  
*Last published:* 2010

**The management of depression during pregnancy**

*Published by:* American Psychiatric Association; American College of Obstetricians and Gynecologists  
*Last published:* 2009

### Oceania

**Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders**

*Published by:* The Royal Australian and New Zealand College of Psychiatrists  
*Last published:* 2015
## Online resources

1. Cornell Scale For Depression in Dementia *(external link)*

2. Edinburgh Postnatal Depression Scale *(external link)*

3. UK Teratology Information Service *(external link)*

4. TOXNET: LactMed *(external link)*
Evidence scores

1. Depressive symptoms: there is medium-quality evidence that a combination of pharmacotherapy and psychotherapy improves 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 reduces the proportion of people who relapse at 1 to 3 years compared with placebo.
   **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 improves depressive symptoms compared with no treatment in older adults in an outpatient or community setting.
   **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.[111]
   **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 improves depressive symptoms over 1 to 6 weeks of 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 re-uptake inhibitors, monoamine oxidase inhibitors, or venlafaxine) are 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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<tr>
<th>Reference</th>
<th>Title</th>
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<th>Year</th>
<th>Page</th>
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Depression in adults

References


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211. Maki PM, Kornstein SG, Joffe H, et al; Board of Trustees for The North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression


Depression in adults


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