BMJ Best Practice

Depression in adults

Straight to the point of care

Last updated: Mar 19, 2025

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Summary

Depression can describe both a mood and an illness.

Major depressive disorder is a clinical syndrome involving mood, neurovegetative functions, cognition, and behaviour.

Depressive disorders are very common and are among the leading causes of disability and excess mortality worldwide.

Risk factors include prior depression and a family history of depression. A history of adverse childhood experiences, 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, psychological therapy, or a combination of both. Watchful waiting may be a suitable approach for some people with milder symptoms. Treatment is personalised, and takes into account patient choice, previous treatment history, treatment availability, severity of depressive symptoms, and psychiatric comorbidities.

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]

Both International Classification of Diseases (ICD)-11 and Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR) define ‘mild’, ‘moderate’, and ‘severe’ depression based on the number and intensity of symptoms, and on the degree of functional impairment.[1] [2] However within clinical practice as well as within clinical trials, there is variability in how different levels of severity of depression are defined.[3] Globally, the most widely used tool for assessing severity of depression in clinical practice is the 9-item version of the Patient Health Questionnaire (PHQ-9), which is based on DSM criteria; scores may be used to characterise severity of depression, and to assess treatment response.[4]

There is no subthreshold (minor) depression diagnosis in DSM-5-TR, but the label has sometimes been applied to diagnose a patient with two to four depressive symptoms, including depressed mood or anhedonia, lasting longer than 2 weeks.[5] [6]

Persistent depressive disorder (termed ‘dysthymic disorder’ within ICD-11) is characterised by at least 2 years of a depressed mood for most of the day, for more days than not, for at least 2 years.[1] [2] See Persistent depressive disorder .

THEORY

Epidemiology

Depressive disorders are very common and are among the leading causes of disability and excess mortality worldwide.[17] [18] [19] [20] In people aged 15-29 years, depression is the leading cause of disability and premature death globally. [WHO: Global Health Estimates] (https://www.who.int/data/global-health-estimates) In the US, major depression is the second leading cause of disability overall.[21] Beyond the direct impact of depression itself on occupational function and quality of life, depression is associated with poorer health outcomes across several conditions.[22] [23] [24]

It has been estimated that around 4.7% of the world's population will experience an episode of depression in any 12-month time period.[25] One international study carried out in 2019 found that point prevalence was highest in North America (4.4% for women and 2.5% for men), lowest in the Western Pacific (2.3% for women and 1.3% for men) and intermediate in other world areas (2.8% to 3.6% for women, and 1.9% to 2.0% for men). [IHME: Global Burden of Disease (GBD)] (https://www.healthdata.org/research-analysis/gbd) In 2015, the World Health Organization (WHO) found a relatively higher 12-month prevalence than this for people living in Africa compared to in other locations globally (5.8% for women, and 4.8% for men).[17] Other studies suggest more substantial variation in reported prevalence between countries, from 2% to 21%, depending on the particular country.[26] Within Europe, prevalence rates vary substantially between countries; higher rates of prevalence have been identified in Germany, Luxembourg and Iceland, with lower rates identified in Slovakia and the Czech Republic.[27] Methodological differences are believed to account for at least some of this reported variability across populations.

Mean age of onset is 26 years in high-income countries, and 24 in low- and middle-income countries, according to World Mental Health survey data.[28] Prevalence peaks again in later life.[29] Global prevalence in older adults has been estimated at 13.3%.[30] Prevalence may be higher amongst older people who are hospitalised or living in assisted care facilities.[31] About one in five nursing home residents without dementia are diagnosed with depression.[32] One systematic review looking at rates of depression in older adults globally, estimated the pooled prevalence of depression in older adults as being 31.74%, with higher rates of depression in this age group seen within developing countries (40.78%) compared to developed countries (17.05%).[31]

Incidence in women is double the incidence in men.[27] [33]

People with depression experience an almost 20-fold risk of dying by suicide than do the general population.[34] One meta-analysis found that 31% of people in treatment for major depressive disorder had attempted suicide in their lifetime.[35]

Comorbidity with other mental health conditions is common across treatment settings in both primary and secondary care, particularly with anxiety disorders, post-traumatic stress disorder and substance use disorders.[36] [37] Men with depression are twice as likely as women to have a comorbid substance use disorder.[38]

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.[39]

Depression frequently coexists with a large number of chronic physical health disorders, including chronic pain, cardiovascular disease, cancer, diabetes, chronic respiratory diseases, tuberculosis, and obesity, potentially as a result of shared risk factors and also due to the causal effect of the physical disorder on the development of depression.[40] Dementia, by some measures, can nearly double the risk.[41] It has been

postulated that depression itself may act as a causal risk factor for the development and worsening of some chronic physical disorders.[42] [43] [44] [45]

The prevalence of major depressive disorder increased rapidly during the COVID-19 pandemic, particularly in younger adults.[46] [47] [48] The World Health Organization (WHO) estimates that the COVID-19 pandemic triggered a 25% increase in the prevalence of depression worldwide; the longer-term implications of this are currently unclear.[49]

Aetiology

The aetiology of depression remains poorly understood. Integrative models, taking into account biological and social variables, most effectively reflect the complex aetiology. It is considered likely that there is substantial heterogeneity amongst causative factors across individuals with depression.[28]

There is evidence for familial risk for depression, but specific genetic factors are still under investigation.[50] Genetic risk is thought to be polygenic, resulting from the combined small effects of a large number of common genetic variants.[51] [52] [53] [54]

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 with depression who have experienced significant life stress.[55] [56] It has been postulated that exposure to adverse life events in early life may lead to epigenetic modifications affecting gene expression, which may predispose to depression.[57] With or without a known genetic component, stressful life events, personality, and sex may also play a modifying role in depression risk. In particular, adversity or maltreatment during critical periods in early life has been demonstrated to substantially increase the risk of later development of depression, and is also associated with a less favourable course of illness, including an increased risk of recurrent depression.[58] [59] Traumatic experiences in adulthood, including intimate partner violence and gender-based violence, also increase the risk of depression.[26]

Previous substance use (particularly cannabis and tobacco) is associated with an increased risk of depression, although this link is not necessarily causal.[60]

Meta-analysis evidence suggests an association between lifestyle habits (including low levels of physical activity and unhealthy dietary pattern) and the development of depression, although it has not been established whether this link is causal.[61] [62][63]

The role of the gut microbiome in the aetiology of depression is an area of active research. Studies have shown differences in the composition of gut microbiota, with associated differences in gut amino acid metabolism, between people with depression and healthy controls.[64] [65]

Pathophysiology

The pathophysiology of depression remains unclear. 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, low levels of noradrenaline (norepinephrine) and dopamine may play a role in the fatigue and hypersomnia, and impaired noradrenaline and serotonergic regulation may contribute to physical symptoms.[66] [67] [68] In particular, the role of serotonin in the development of depression has been much-studied, but remains incompletely understood. Older explanations that attribute depression to a 'deficiency of serotonin' are now widely regarded as overly simplistic and misleading. A large, widely reported umbrella review challenged the role of serotonin in depression, although these findings have been questioned by other experts, citing possible methodological weaknesses.[69] [70] Perhaps the most resilient experimental evidence for the hypothesis that low serotonin is associated with depression comes from studies using the tryptophan depletion method - effectively depleting bodily tryptophan and therefore serotonin by ingesting a cocktail containing all amino acids except tryptophan. This method tends to temporarily restore depressive symptoms in patients who have recovered from major depression. The effect appears to be limited to those in recovery from depression, not in volunteers without depression, so the role of serotonin in causing depression, if any, appears complex.[71] [72]

HPA axis dysregulation has been demonstrated in people with depression. Morning cortisol secretion is not suppressed by administration of low-dose dexamethasone at bedtime in many people with depression.[73] [74]

Gut microbiota alterations are hypothesised to influence mood by production of metabolites and bacterial components that affect neurotransmission in the central nervous system; animal models offer tentative evidence in support of this theory.[64] [65] [75]

Systemic inflammation has been proposed as one potential causative factor in the pathogenesis of depression; of note, there is some evidence that previous childhood maltreatment increases the risk of systemic inflammation in adults.[76]

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, and reduction in hippocampus volume.[77] [78] [79] Structural and functional abnormalities in fronto-limbic networks were also detected in neuroimaging studies of treatment-naive patients with depression.[80] [81] However, findings vary substantially across individuals, underscoring clinical heterogeneity. Depression is postulated to be the result of dysfunction across interconnected networks in the brain, and the aim of much current research is to explore neural systems, rather than individual brain regions.[82]

Classification

International classification of diseases, eleventh edition (ICD-11)[2]

ICD-11 depressive disorders are subdivided into single-episode and recurrent types, with designations for severity of the most recent episode and, in severe cases, the presence or absence of psychosis (hallucinations or delusions).

Additionally, ICD-11 includes under the depressive disorder category a diagnosis of dysthymic disorder and a new one for mixed anxiety and depressive disorder

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

DSM-5-TR divides depressive disorders into:

- Disruptive mood dysregulation disorder
- Major depressive disorder (including major depressive episode)
- Persistent depressive disorder (previously known as dysthymic disorder)
- Premenstrual dysphoric disorder
- Substance-/medication-induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorders
- Unspecified depressive disorder
- Unspecified mood disorder.

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

Case history

Case history #1

A 35-year-old woman presents with a 1-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 two 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

Although core features of depression appear to be relatively consistent across different cultures, a number of key points of cultural variation have been noted; for example, sadness may be less of a prominent symptom in some cultures, and differences in expressing emotions may result in underreporting of emotional and cognitive symptoms in some cultural groups compared to somatic symptoms.[7] Somatic symptoms (e.g. headaches, generalised aches and pains, palpitations, tremor, blurred vision), although not comprehensively described in current established diagnostic criteria, are commonly reported symptoms of depression across a number of different geographical populations, including people from Africa, Asia, Central and South America and the Pacific Islands, but may occur in people with depression regardless of their location or culture.[8] [9]

In a minority of people with depression, and more commonly in men, externalising features may be present, for example, anger, aggression, substance use problems, and risk-taking behaviour.[10]

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. Older people may also be more likely to have single or multiple comorbidities

that contribute to the development of depression (e.g., malaise from medical illness or side effects of non psychiatric medications).[11]

Women in the perinatal period are at high risk for depression.[12] See Postnatal depression .

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.[13] [14] [15] [16]

Approach

Depression is the most common psychiatric disorder in the general population; the majority of people with depression will present initially to primary care.[124] [125] The initial diagnosis may be missed in as many as 50% of people with depression in this setting.[126] [127]

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 with mild depression may appear to be functioning normally, but this requires considerably increased effort.[1] Fatigue and sleep disturbance are common features of depression. Psychomotor disturbances, and delusional (or near-delusional) guilt, are much less common but indicate greater overall severity when present.[1] Some patients emphasise somatic complaints rather than feelings of sadness.[1]

Patients may report psychotic symptoms such as delusions or hallucinations.[1] [2]

Patients often have a personal or family history of depression. Enquire about the patient's response to any past psychiatric treatments (including pharmacological and non-pharmacological treatments), any history of psychiatric hospitalisation, and any emergency department visits for psychiatric illness.[128]

Some patients will have experienced stress, trauma, or loss. Clinicians should use open-ended, empathic questions when enquiring about a patient’s trauma history.[128] Patients may not share details of childhood physical or sexual abuse unless specifically asked.[128]

In older patients, depression can present as diminished self-care, somatic complaints, psychomotor retardation, irritability, and apathy. These patients may also present with severe cognitive disturbance (memory deficits) as a result of the depression.[31] Older patients may also be more likely to have single or multiple comorbidities that contribute to the development of depression (e.g., malaise from medical illness or side effects of non-psychiatric medications).[11]

Risk of death by suicide is increased substantially, with an almost 20-fold increase in risk compared to the general population.[34] Suicide risk mitigation 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.[129] See Suicide risk mitigation .

Substance use is common in people with depression.[38] [104] Enquiry should should include assessment of alcohol, tobacco, recreational drugs, and any misuse of prescribed or over-the-counter medications.[128]

Enquire about other psychiatric and non-psychiatric diagnoses. Some physical illnesses may cause symptoms that mimic depression (e.g., hypothyroidism, Cushing's disease). Depression may also affect a patient’s ability to adhere to treatment for a physical illness.

Examination

There are no definitive findings of depression on physical examination. Many patients will have a depressed affect. Some will have 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 Depression for use in the perinatal period.[130] [131] [Edinburgh Postnatal Depression Scale] (https://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf) Several diagnostic tools are available for older adults, such as the Geriatric Depression Scale and, when cognitive impairment is prominent, the Cornell Scale for Depression in Dementia. [Cornell Scale For Depression in Dementia] (https://cgatoolkit.ca/Uploads/ContentDocuments/cornell_scale_depression.pdf)

Screening tools validated in an appropriate language for the patient may be required.

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.[132]

Depression diagnosis

To ensure diagnostic accuracy, physicians should apply International classification of diseases, eleventh edition (ICD-11) or Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR) 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. See Criteria . Subthreshold (minor) depression is not defined in DSM-5-TR, but may apply to those with 2-4 depressive symptoms, including either sad mood or anhedonia, for at least 2 weeks.[5] [6]

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.[133] 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 or, for older people with cognitive impairment, the Cornell Scale for Depression in Dementia. [Cornell Scale For Depression in Dementia] (https://cgatoolkit.ca/Uploads/ContentDocuments/cornell_scale_depression.pdf) Physicians can use the PHQ-9 to score current depression severity and to follow up treatment response.

Tests

Depression is a clinical diagnosis. There are no diagnostic tests.[134] 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.

History and exam

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, myocardial infarction, and obesity); personal or family history of depression; certain medications (e.g., corticosteroids) and female sex.

depressed mood (common)

- Major criterion for diagnosis: depressed mood or loss of interest, most of the day, nearly every day, for a period of 2 weeks along with 4 other symptoms of depression.[1]

anhedonia (common)

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

functional impairment (common)

- Symptoms cause impairment in, for example, social or occupational functions.[1]

Other diagnostic factors

weight change (common)

- Significant weight loss when not dieting, weight gain, or decrease or increase in appetite nearly every day.[1] A change of >5% of body weight within 1 month is considered significant.[1]

libido changes (common)

- May show reduced libido.

sleep disturbance (common)

- Insomnia or hypersomnia persistently.[1]

changes in movement (common)

- Psychomotor agitation or retardation nearly every day.[1] The changes in movement should be observable by others, rather than subjective feelings of restlessness or being slowed down.[1]

low energy (common)

- Fatigue or loss of energy nearly every day.[1]

excessive guilt (common)

- Feelings of worthlessness or excessive or inappropriate guilt nearly every day.[1]

poor concentration (common)

- Diminished ability to think or concentrate, or indecisiveness, nearly every day.[1]

suicidal ideation (common)

- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a specific suicide plan, or a suicide attempt.[1]

somatic symptoms (common)

- Somatic symptoms (e.g., headaches, generalised aches and pains, palpitations, tremor, blurred vision), although not comprehensively described in established diagnostic criteria, are commonly reported symptoms of depression, particularly in certain geographical populations, for example, people from Africa, Asia, Central and South America, and the Pacific Island, but may occur in people with depression regardless of their location or culture.[8] [9]

bipolar disorder excluded (common)

- According to DSM-5-TR, there should be no evidence of mania or hypomania.[1]

substance abuse/medication side effects excluded (common)

- According to DSM-5-TR, 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.[1]

medical illness excluded (common)

- According to DSM-5-TR, major depressive disorder should not be diagnosed if the symptoms are primarily attributable to a somatic medical condition.[1]

schizophrenia excluded (uncommon)

- According to DSM-5-TR, chronic psychosis excludes the diagnosis of major depressive disorder if the depressive symptoms are primarily attributable to the chronic psychotic illness.[1]

Risk factors

Strong

postnatal status

- Approximately 19% of postnatal women have a major depressive episode during the first 3 months after delivery.[83] Women with a previous psychiatric disturbance, poor social support, and an unplanned pregnancy are at higher risk.[12] Parenting programmes may improve the short-term psychosocial health of mothers.[84] See Postnatal depression .

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.[85] The rate of suicide is twice as high in families of suicide victims.[86]

history of an anxiety disorder, or anxiety symptoms

- Anxiety and depressive disorders are highly comorbid; according to one worldwide survey, 45.7% of people with major depressive disorder had a history of one or more anxiety disorders. Comorbidity with an anxiety disorder during depressive episodes was also common, occurring in 41.6% of people with depression.[87] According to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 53% of the patients with major depression also had significant symptoms of anxiety (often termed 'anxious depression').[88]

adverse childhood experiences

- Adversity or maltreatment during critical periods in early life has been demonstrated to substantially increase the risk of later development of depression, and is also associated with a less favourable course of illness, including an increased risk of recurrent depression; however, some studies suggest that antidepressant treatment can nevertheless be helpful in this population.[58] [59][89] The risk is not entirely psychological: it has been postulated that exposure to adverse events in early life may lead to epigenetic modifications affecting gene expression, which may predispose to depression.[57] Childhood adversity is also associated with increased risk of depression in people who have particular alleles of the polymorphic FKBP5 gene, which encodes a protein involved in glucocorticoid signaling pathways.[56]

dementia

- In older adults with dementia, the prevalence of comorbid depression appears to be around 16%, although may be as high as 35% depending on the diagnostic criteria used; dementia, by some measures, can nearly double the risk of depression in older adults.[41] Depression may be a prodromal feature of dementia, or a psychological response to experiencing a degenerative disease with associated loss of function and autonomy.[90] Conversely, depression may also be a risk factor for dementia.[91]

corticosteroid use

- Depression is a documented adverse effect.[92]

interferon use

- Depression is a documented adverse effect and is treatable.[93]

oral contraceptive use

- A large population-based study found a slight, but statistically significant elevated risk of depression in oral contraceptive users.[94] Risk appears to vary by age and hormone contents of the specific oral contraceptive.[95]

co-existing medical conditions

- Patients hospitalised for medical or surgical problems and those 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.[13] [14] [15] [16] [96] [97] [98] [99] [100] [101] There may be a particularly increased risk of depression in chronic illness in patients with conditions characterised by inflammation and pain.[102] The relationship between chronic medical conditions and depression is bidirectional. Depressed patients are more likely to develop chronic medical conditions.[43] [44] Adults who experienced chronic medical illness in childhood also have higher rates of depression.[103]

female sex

- Incidence of depression in women is double the incidence in men.[27] [33]

Weak

comorbid substance use

- The use of intoxicating substances (alcohol, cannabis, and other recreational drugs), often to an excessive or habitual degree, is common in people with depression.[38] [104] [105] Men with depression are twice as likely as women to have a comorbid substance use disorder.[38] There is no evidence that medical cannabinoids are effective for the treatment of depression.[106]

personality disorders

- Some personality disorders co-occur more frequently with depression, including borderline personality disorder, and Cluster C personality disorders.[107] [108] [109] Depression combined with a personality disorder may have a poorer outcome than depression alone; however, data are mixed.[110]

history of violent victimisation

- Having been the victim or witness of violence, such as physical or sexual abuse including intimate partner violence, is a risk factor for subsequent development of depression.[26] [111]

obesity

- New data analytic methods applied to several very large databases have supported the hypothesis that body fat mass is associated with, and likely a causal factor for, depression.[112] One population-based study conducted in Europe reported a significantly higher prevalence of depression in people with BMI >30 kg/m² compared with people with BMI >18.5 kg/m² and <30 kg/m².[27]

older age (≥65 years)

- Rates of depression increase in older-age, particularly among older people who are hospitalised or living in assisted care facilities.[31] Global prevalence in elderly people has been estimated at 13.3%.[30] Another systematic review looking at rates of depression in older adults globally, estimated the pooled prevalence of depression as being 31.74%, with higher rates of depression seen within developing countries (40.78%) compared to developed countries (17.05%).[31]

separated/divorced marital status

- Associated with an increased risk of developing major depressive disorder according to one systematic review.[26]

Investigations

1st test to order

Test	Result
clinical diagnosis • Major depression: ≥5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure: depressed mood most of the day, nearly every day as self-reported or observed by others; markedly 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, or indecisiveness, nearly every day; recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a specific suicide plan, or a suicide attempt.[1] • 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-5-TR 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 had depressed mood, for most of the day, for more days than not, for ≥2 years.[1] • Subthreshold (minor) depression is not defined in DSM-5-TR, but may apply to those with 2-4 depressive symptoms, including either sad mood or anhedonia, for at least 2 weeks.[5] [6]	**ICD-11 or DSM-5-TR diagnostic criteria depending on the depressive subcategory**
metabolic panel • Provides baseline and may reveal metabolic disturbance.	**normal**
FBC • Other causes of fatigue such as anaemia should be ruled out.	**normal**
thyroid function tests • An elevated serum thyroid-stimulating hormone level suggests hypothyroidism.	**normal**

Test	Result
Patient Health Questionnaire-2 (PHQ-2) • The 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: '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?'[135] • A positive response to either question warrants a thorough review of diagnostic 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-TR 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 • US and UK guidelines stress the importance of routinely assessing patients for depression during the perinatal period.[136] [137] The Edinburgh Postnatal Depression Scale is a 10-item questionnaire for women in the perinatal period. A score of ≥10 suggests depression; however, clinicians should be mindful of individual patient circumstances (e.g., education and culture) that might impact scoring.[138] [139] [140] Although it does not assess the severity of depression, it does assess for suicidal ideation. [Edinburgh Postnatal Depression Scale] (https://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf) • See Postnatal depression .	**positive result screens for depression in postnatal period**
Geriatric Depression Scale • The short form contains 15 yes/no questions. • This scale does not assess the severity of symptoms.[141] [142]	**>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] (https://cgatoolkit.ca/Uploads/ContentDocuments/cornell_scale_depression.pdf) • This scale does not assess the severity of symptoms.[143]	**>10 suggests probable depression; >18 indicates definite depression**

Other tests to consider

Test	Result
24-hour free cortisol • Elevated 24-hour urinary free cortisol level suggests Cushing's disease.	**normal**
vitamin B12 • Vitamin B12 deficiency is associated with macrocytic anaemia, paraesthesia, numbness, and impaired memory.	**normal**
folic acid • Patients with depression have been found to have lower levels of serum folate than people without a psychiatric diagnosis, and than non-depressed psychiatric patients.[144]	**normal**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Adjustment disorder with depressed mood	• 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.	• DSM-5-TR.
Substance-/medication-or medical illness-associated and other depressive disorders	• 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.	• 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.
Bipolar disorder	• In this condition, major depressive disorder is accompanied by or interspersed with one or more manic, hypomanic, or mixed episodes.	• ICD-11, DSM-5-TR.
Premenstrual dysphoric disorder (PMDD)	• PMDD is characterised by depressed mood, anxiety, and irritability during the week before menses and resolving with menses. PMDD also has prominent pain symptoms.	• ICD-11, DSM-5-TR.
Grief/bereavement	• Depressive symptoms may be transiently present in normal grief. The duration and expression of normal grief varies among racial/ethnic groups.[145] • 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	• ICD-11, DSM-5-TR.

Condition	Differentiating signs / symptoms	Differentiating tests
	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. • Note that ICD-11 introduced prolonged grief disorder as a new diagnostic category, which describes a pathologically persistent and disabling reaction to bereavement, exceeding social, cultural and religious norms.[2] • According to DSM-5-TR and ICD-11, 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.[146]	
Dementia	• Dementia is characterised by cognitive (memory) changes, psychiatric symptoms, personality changes, problem behaviours, and changes in day-to-day functioning.	• A mini-mental state examination or neuropsychiatric testing should be conducted if the diagnosis is uncertain.[147] • Focused laboratory testing (i.e., thyroid-stimulating hormone level, vitamin B12 level) should be considered for reversible causes of dementia.
Anxiety disorders	• Anxiety disorders frequently occur along with depression. Generalised anxiety disorder (GAD) is characterised by excessive worry, muscular tension, fatigue, autonomic hyperactivity, and increased vigilance; patients with anxious depression may	• ICD-11, DSM-5-TR.

Condition	Differentiating signs / symptoms	Differentiating tests
	appear to have GAD.[148] Specific anxiety disorders (i.e., panic disorder, social phobia, obsessive-compulsive disorder, PTSD) should also be considered.	
Alcohol-use disorder	• Patients often may complain of insomnia, nightmares, poor memory, and nervousness.	• Various screening tools are in wide use, including the CAGE questionnaire and the Alcohol Use Disorders Identification Test (AUDIT).[149]
Anorexia nervosa	• 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.	• ICD-11, DSM-5-TR.
Hypothyroidism	• Associated signs and symptoms include weight gain, constipation, and fatigue.	• An elevated serum thyroid-stimulating hormone level suggests hypothyroidism.
Medicine adverse effects	• Patients should be asked about use of glucocorticoids, interferon, levodopa, propranolol, and oral contraceptives. Results from studies investigating whether isotretinoin increases the incidence of depression and/or suicidal ideation are conflicting; signs and symptoms of depression should be monitored during and after treatment with isotretinoin.[150]	• These effects may be temporally associated with medicine initiation race.
Cushing's disease	• This disease is associated with progressive obesity, dermatological manifestations, signs of adrenal androgen excess, and proximal muscle wasting.	• Elevated 24-hour urinary free cortisol level.
Vitamin B12 deficiency	• This deficiency is associated with macrocytic anaemia, paraesthesia, numbness, and impaired memory.	• Reduced serum vitamin B12 level.

Condition	Differentiating signs / symptoms	Differentiating tests
Obstructive sleep apnoea (OSA)	• Depressive symptoms are a common consequence of OSA, and can be reversed by treatment directed at the OSA.[151]	• Sleep study.

Criteria

International classification of diseases, eleventh edition (ICD-11)[2]

ICD-11 depressive disorders are subdivided into single-episode and recurrent types, with designations for severity of the most recent episode and, in severe cases, the presence or absence of psychosis (hallucinations or delusions).

Symptoms include:

- Depressed mood
- Diminished interest/capacity for pleasure
- Change in sleep
- Psychomotor change
- Reduced energy; fatigue
- Feelings of worthlessness; excessive or inappropriate guilt
- Hopelessness
- Difficulty concentrating
- Recurrent thoughts of death or suicide.

Mild depression is diagnosed when no symptom is present to an intense degree and there is some, but not considerable, functional impairment.

Moderate depression denotes several symptoms present to a marked degree and considerable but not complete functional impairment.

Severe depression is diagnosed when many or most of the characteristic symptoms of depression are present to a marked degree, and/or several are present to an intense degree, and there is complete or near-complete functional impairment.

Note: the presence of psychotic symptoms by definition defines an episode as moderate or severe.

Additionally, ICD-11 includes under the depressive disorder category a diagnosis of dysthymic disorder, and a new one for mixed anxiety and depressive disorder.

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

DSM-5-TR divides depressive disorders into:

- Disruptive mood dysregulation disorder
- Major depressive disorder (including major depressive episode)

- Persistent depressive disorder (previously known as dysthymic disorder)
- Premenstrual dysphoric disorder
- Substance-/medication-induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorders
- Unspecified depressive disorder
- Unspecified mood disorder.

Major depression[1]

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

- Depressed mood most of the day, nearly every day, as self-reported or observed by others
- Markedly diminished interest or pleasure in all or almost all activities, for 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, or indecisiveness, nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a specific suicide plan, or a suicide attempt.

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-TR:

- Mild: few, if any, symptoms more than number required for diagnosis of major depression, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor functional impairment
- Moderate: the number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for ‘mild’ and ‘severe’ depression
- Severe: the number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.

The following specifiers may be added to the diagnosis of depressive disorder:

- With anxious distress
- With mixed features (if there are at least 3 associated manic/hypomanic symptoms)
- With melancholic features
- With atypical features
- With psychotic features
- With catatonia

- With peripartum onset
- With seasonal pattern.

Depressive disorder (subthreshold or minor depression)

Subthreshold (minor) depression is not defined in DSM-5-TR, but when used in the past it referred to a patient who had from 2-4 depressive symptoms, including either sad mood or anhedonia for at least 2 weeks.[5]

Depressive disorder due to:

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

Persistent depressive disorder[1]

Depressed mood, for more days than not, for ≥2 years. Impairment compared with major depressive disorder may be less severe. During the 2 years, the patient has never been without symptoms for more than 2 months at a time.

Two or more of the following symptoms are present while depressed:

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

Screening

Recommendations

The US Preventive Services Task Force (USPSTF) found convincing evidence to recommend screening for depression in the general adult population, including pregnant and postnatal women and older adults, although public health bodies in some countries (e.g., the UK and Canada) do not recommend routine screening.[132][152] [153] Systems should be in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up after screening. There was insufficient evidence to support universal screening of suicide risk directly.[132]

There are some clinical situations in which routine screening is recommended. For example, because of the high risk for depression after physical trauma, a brief screening instrument like the Patient Health Questionnaire-2 (PHQ-2) or Patient Health Questionnaire-9 (PHQ-9) should be administered to patients admitted to trauma centres, according to US-based guidance.[154] Regular routine screening and

assessment for depression is recommended for patients with cancer in all phases of the illness, according to European treatment guidelines.[155]

Tools

The 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:[135]

'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 Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR) criteria or an equivalent tool.

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-TR 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.

One meta-analysis determined that a screening approach beginning with a PHQ-2, and moving on to a PHQ-9 for PHQ-2 scores of ≥2, was similarly accurate to administering the PHQ-9 to all patients, and reduced the need to administer a full PHQ-9 by over 50%.[156]

Screening in pregnancy

Evidence suggests that screening pregnant and postnatal women reduces the risk of depression.[157] [158] The US guidelines stress the importance of routinely assessing patients for depression during the perinatal period. The American College for Obstetricians and Gynecologists (ACOG) recommends that screening for perinatal depression takes place at multiple timepoints during the perinatal period using the same standardised, validated screening instrument; this includes the initial antenatal visit, later in pregnancy, and at postnatal visits. Examples given include the Edinburgh Postnatal Depression Scale (EPDS) or Patient Health Questionnaire (PHQ-9).[136]

This EPDS is a 10-item questionnaire that is commonly used in the perinatal period. A score of ≥10 suggests depression.[138] [139] [140] One meta-analysis determined that a cut-off score of 13 or more identified higher-severity cases, while a cut-off score of 11 or above optimised sensitivity and specificity in screening.[159] EDPS includes an assessment of suicidal ideation. [Edinburgh Postnatal Depression Scale] (https://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf)

ACOG recommends that, when someone answers ‘yes’ to a self-harm or suicide question in the perinatal period, clinicians should immediately assess for likelihood, acuity, and severity of risk of suicide attempt and then arrange for risk-tailored management.[136] See Suicide risk mitigation .

Canadian guidance recommends against universal instrument-based screening during the perinatal period, but assumes that, as part of usual care during the perinatal period, care providers will inquire about and be attentive to maternal health and well-being.[160] The UK National Institute for Health and Care Excellence (NICE) recommends that healthcare professionals (including midwives, obstetricians, health visitors, and general practitioners) should consider asking two questions to identify possible depression in the perinatal period, at the woman's first contact with primary care, at her first antenatal appointment (usually around week 10 of pregnancy), and postnatally (first year after childbirth):[137]

- During the past month, have you often been bothered by feeling down, depressed, or hopeless?
- During the past month, have you often been bothered by having little interest or pleasure in doing things?

If the woman answers 'yes' to either of the initial questions, is at risk of developing a mental health problem, or there is clinical concern, NICE recommends that clinicians consider:

- Using the EPDS or
- Using the PHQ-9 as part of a full assessment or
- Referring the woman to her GP, or, if a severe mental health problem is suspected, to a mental health professional

Women at high risk for depression because of a prior or current history of severe depressive disorder should ideally be under the care of a specialist perinatal psychiatrist; clinicians should ask about depressive symptoms at each contact.[137]

For specific information on screening for depression in the postnatal period, see Postnatal depression .

Screening in older adults

The Geriatric Depression Scale and Cornell Scale for Depression in Dementia have been validated for older adults with and without dementia, respectively.[141] [142] [143]

Approach

The goals of treatment are to eradicate symptoms of depression, improve daily functioning and quality of life, improve workplace functioning, reduce suicidality, minimise treatment adverse effects, and prevent relapse.[161] [162][163]

The initial priority is to identify and mitigate against any immediate risks for harm to self or others, including consideration of the need for inpatient admission (see Acute and urgent considerations).

For people with depression who can be safely managed outside of a hospital setting, first-line treatment options include:[164] [165]

- Psychological therapy (e.g., cognitive behavioural therapy [CBT])
- Pharmacotherapy (e.g., antidepressants)
- The combination of psychological therapy and pharmacotherapy

Both antidepressants and psychological therapy have shown effectiveness when used alone, and yield similar results in randomised trials. Results from one meta-analysis of antidepressant treatment for adults with depression suggest numbers needed to treat (NNT) values of 16, 11, and 4 for the mild-to-moderate, severe, and very-severe subgroups, respectively.[166] Psychological treatments have been shown to be both effective and cost-effective in reducing depressive symptoms, and may reduce the number of sickness absence days from work, whether this is face to face or online.[163] [167] [168] [169] Treatment response to CBT is comparable with antidepressant response in some studies.[170] [Evidence B] For those with more severe depression, the combination of psychological therapy plus pharmacotherapy has demonstrated greater efficacy than either treatment alone.[171] [172] [173] [174] Psychological therapy, both used alone or used in combination with pharmacotherapy, has a more enduring treatment effect than pharmacotherapy alone.[175] It should be noted that for people with subthreshold or mild symptoms, the prognosis is often good without the need for pharmacotherapy or psychological therapy.[176]

Electroconvulsive therapy (ECT) may be an option for those who have not responded to, or cannot tolerate, antidepressants.[165] The response rate is better for patients with severe major depression than for moderate or mild depression.[177] The potential impact on memory and cognition, which may reduce functioning during active treatment, make ECT less desirable for patients with less severe depression. ECT is often the treatment of choice for severely depressed people with late-life depression, because it is effective, and avoids complications that may arise from pharmacological intolerance and drug-drug interactions associated with treatment for comorbid physical conditions.[178]

Treatment decisions are informed by a number of important real-world considerations, including access to psychological treatment, which may be limited or non-existent in some locations. Furthermore, people with depression may have a strong preference for either psychological therapy or pharmacotherapy. Research to guide evidence-based individualised treatment is at an early stage.[179] Choice of treatment is therefore highly individualised and empirically validated.

For all patients with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and it may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as ‘laziness’ or disinterest.[180]

Lifestyle advice encompassess instruction on the following:[180]

- Sleep hygiene, and setting appropriate times for sleeping and waking
- Healthy diet and exercise
- Cessation of smoking, excess intake of alcohol and substance misuse (including cannabis use); if cessation is not possible, then advice on moderation is required

Urgent and acute considerations

Features indicating a need for urgent management include psychosis, suicidal ideation, catatonia, severe psychomotor retardation impeding activities of daily living, and severe agitation.[165] [181] [182] These people 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, tranquilisation, and/or ECT may be required to ensure safety 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 Moore severe depression.

Urgent consultant referral is indicated and hospitalisation should be considered for people:[165] [181] [182]

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

Suicide risk mitigation

- Suicide risk mitigation is critical, especially as the risk may increase early in treatment. Routinely asking people about suicidal ideation and reducing access to lethal means (especially firearms) can reduce the risk of suicide.[129] Close telephone follow-up by a trained psychiatrist may help reduce the risk of death by suicide after a previous suicide attempt.[183] See Suicide risk mitigation .

Pharmacotherapy

- Antidepressant therapy: usually the first-line option in most people with severe depression requiring an urgent management approach. General principles of prescribing antidepressants are described in 'More severe depression'.
- Psychosis: antidepressants alone may not effectively address psychotic symptoms, such as delusions or hallucinations; therefore, clinicians should have a lower threshold for adding an antipsychotic to antidepressant treatment in people with psychosis.[165] [184] [185]
- Agitation: for people who have severe agitation as a depressive symptom, antipsychotics can directly tranquilise the distress associated with this form of severe depression. People with agitation may also benefit from short-term treatment with a benzodiazepine, or possibly both an antipsychotic and a benzodiazepine, until definitive antidepressant therapy takes effect.[186] Patients with mild agitation or severe anxiety can be treated with a benzodiazepine and/or an antipsychotic.
- Catatonia: people with catatonia are usually treated with a benzodiazepine, sometimes in combination with an antipsychotic: ECT may also be considered.[187]
- Suicidality: esketamine nasal spray (an active isomer of ketamine, an N-methyl-D-aspartate [NMDA] receptor antagonist) may be considered by a consultant for those with depression with acute suicidal ideation or behaviour, as an adjunct therapy to an oral antidepressant. Although

esketamine is being used more frequently in clinical practice, questions remain about which patients respond best to it, how long therapeutical effects might persist, and over what duration to continue treatment. While no longer considered a last-resort treatment, esketamine is not a first- or second-line treatment, and it is typically reserved for people with persistent suicidal ideation. Availability of esketamine varies according to country of practice and relevant regulatory approval. In the US, the drug is only available through a restricted distribution programme. 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, respiratory depression, 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. Esketamine is contraindicated in patients with aneurysmal vascular disease, arteriovenous malformation, or intracerebral haemorrhage. Use of esketamine nasal spray beyond 4 weeks is not currently supported by evidence, given that its effectiveness beyond 4 weeks has not yet been evaluated. Esketamine may also be considered for some people with treatment-resistant depression (see below).

Electroconvulsive therapy (ECT)

- Indication: although most people referred for ECT have tried other antidepressant treatments, ECT may be considered early in the course of treatment in certain people with severe depression. It may be used early in treatment for depression with psychotic symptoms, suicidality, or catatonia, or where there has been a previous positive treatment response to ECT.[165] [177]
- General procedure: ECT is performed under general anaesthesia, typically 2 or 3 times a week for a total of 6-12 treatments.[188]
- Risks: patient and clinician must be fully informed of the potential risks, including the risks associated with not having ECT, so that the patient can provide informed consent.[165] The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments, meaning that it is one of the safer procedures performed under general anesthetic.[189] [190] Overall, there is no increase in risk of medical complications in patients receiving ECT versus equally depressed patients not receiving ECT.[191] ECT affects heart rate and blood pressure. Chest pain, arrhythmias, persistent hypertension, and ECG changes have been reported as complications, particularly in patients with pre-existing cardiac disease.[192] Cardiovascular conditions should be stabilised before administering ECT.[192] 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.[193] [194] This potential risk must be balanced against the evidence in favour of its efficacy, especially in patients with severe depression. If a person with depression cannot give informed consent for ECT, it should only be given when it does not conflict with a valid advance treatment decision made by the person.[165]
- After-effects: ECT treatment effects are temporary; following successful treatment, the effect must be maintained by the use of antidepressants and/or maintenance electroconvulsive treatments (typically once per week to once every 4 weeks or longer, titrated to stability).[195]

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.

Psychological therapy

- These patients are unlikely to find other talking treatments 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.

More severe depression

'More severe depression' has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of 16 or more.[165] This category includes both moderate and severe depression, as defined by DSM-5-TR.[165]

While it is important to assess the severity of depression using valid diagnostic criteria, the author uses a somewhat broader approach when determining severity of depressive symptoms. Thus the author notes that, within their own clinical practice, the following factors might sway the judgement towards considering a specific depressive episode to be 'more severe':

- Symptoms suggestive of high clinical risk, for example, suicidal ideation
- Symptoms that are highly specific for depression and/or that might impede normal coping strategies, for example, lack of interest[196]
- Symptoms that are present on a daily or near-daily basis
- A substantial lack of motivation where the person is unable to distract themselves from their depressive symptoms

For people with more severe depression who can be safely managed outside of a hospital setting, treatment options include pharmacotherapy and psychological therapy, either alone or in combination.[165] [197] Efficacy of antidepressants is more pronounced with increasing severity of depression.[166] The combination of psychological therapy plus pharmacotherapy has demonstrated greater efficacy for this patient group than either treatment alone.[171] [172] [173] [174] The World Health Organization (WHO) recommends psychological interventions whenever possible for all adults with moderate-to-severe depression, either with or without pharmacotherapy.[198] Although monotherapy with a psychological therapy is one potential option as endorsed by some treatment guidelines, the author notes that evidence to support this approach is limited.[165] [197] [198] [199] In the absence of definitive evidence supporting this approach, clinicians should consider patient preferences or other individual factors when deciding whether to offer psychological therapy alone to people with more severe depression. A stepped care model may be considered, whereby those who do not respond adequately to psychological treatment alone are offered timely add-on pharmacological treatment.[198]

Regardless of treatment type, close follow-up and at minimum supportive or educational interventions during the onset of treatment can improve treatment adherence and 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.

Antidepressants for more severe depression

Antidepressants are more efficacious than placebo in patients with moderate or severe depression.[200] [201]

Choice of antidepressant

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
- Reboxetine (a noradrenaline-reuptake inhibitor)

No consistent differences in safety or efficacy have been demonstrated between antidepressants.[202] [203] While a few meta-analyses of comparative treatment efficacy have favoured one drug over others, by and large they are comparable in efficacy.[204] [205]

US guidance recommends that initial pharmacological treatment should be with a second-generation antidepressant (e.g., SSRI, SNRI, bupropion, mirtazapine, vilazodone, vortioxetine).[197] UK guidance recommends offering an SSRI as first-line treatment for most people with depression for whom pharmacological treatment is suitable.[165] Later-line options recommended by NICE include an SNRI or (in secondary-care only) a tricyclic antidepressant or a monoamine oxidase inhibitor (MAOI).[165] According to UK guidance, clinicians should only consider prescribing vortioxetine when there has been no or limited response to at least 2 previous antidepressants.[165]

Choice of drug should be based on patient preference, tolerability, safety in overdose, presence of other psychiatric illness, and past evidence of effectiveness in the patient.[181]

Determine antidepressant dose based on the known target dose range. Within the recommended ranges for several commonly used second-generation antidepressants (SSRIs, venlafaxine, and mirtazapine) it has been shown that across a population, the correlation between dose and efficacy flattens or declines at around the midpoint, in part because of diminished tolerability at higher doses.[206] High-dose SSRI treatment for depression in patients refractory to medium-dose treatment is not supported by evidence and is not recommended.[207] [208] [209]

Depressed patients with undiagnosed bipolar affective disorder may convert to frank mania if they receive antidepressants. 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.

Antidepressants and suicide risk

Although the net result of antidepressant response is a significant reduction in suicidal ideation, there is some evidence of increased suicidal thoughts and behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[210][211] [212] [213] This association is not necessarily causal and may instead be attributable to confounding factors.[214] 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).[215] Close monitoring and suicide risk mitigation is recommended when prescribing an

antidepressant to a person under the age of 25 years, or to anybody thought to be at increased risk for suicide.[165]

Assessing antidepressant response

Follow up patients 1-2 weeks after initiating therapy, then monthly for the next 12 weeks. The Patient Health Questionnaire-9 (PHQ-9) may be used 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 may begin to show a response within the first 1-2 weeks of treatment; however, one fifth of those who have not previously responded may begin to respond after week 5.[216] Successful antidepressant therapy to the point of remission of all symptoms may be expected to 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.

Psychological treatments for more severe depression

Psychological treatments may be delivered via different methods and settings, and may include individual, group, or virtual sessions. No clear differences in efficacy have been found among different types of psychological therapies used for depression.[217] Published treatment guidelines recommend a range of psychological therapies as first-line options more more severe depression, including cognitive behavioural therapy (CBT), behavioural activation, short-term psychodynamic therapy, interpersonal psychotherapy, and problem-solving therapy.[165] [218] However guidance from the American College of Physicians only recommends CBT, citing insufficient evidence to support other types of psychological therapies.[197]

CBT has shown greater efficacy than pharmacological placebo across levels of severity.[219] Treatment response to CBT is comparable with antidepressant response in some studies.[170] [Evidence B] CBT has an enduring effect that reduces subsequent risk after treatment ends.[175] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[220]

Other psychological modalities for more severe depression include include the following.[165] [218]

- Interpersonal psychotherapy (IPT): requires the patient to have psychological insight.[221] Frequency for IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. IPT may improve interpersonal functioning, and also appears effective for relapse prevention.[222]
- Problem-solving therapy (PST): focuses on training in adaptive problem-solving attitudes and skills.[223] [224] [225] Results from PST are comparable to those from CBT in primary care settings.[226]
- Behavioural activation: 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. A Cochrane review found it to be equally effective to CBT for adults with depression, albeit with a low level of certainty given the evidence available.[227]
- Short-term psychodynamic psychotherapy: may be useful for people with emotional and developmental difficulties in relationships contributing to their depression.[165] [228]

Less severe depression

'Less severe depression' has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of less than 16.[165] This category includes both subthreshold and mild symptoms. Patients

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

For people with subthreshold and mild symptoms, the prognosis is often good without the need for pharmacotherapy or formal psychological therapy.[176] [229] For people with less severe depression who do not want treatment, or who feel that their depressive symptoms are improving, an initial period of active monitoring may be appropriate, with review after 2-4 weeks, with advice given to seek medical input if symptoms worsen, and the option to consider treatment at any time if needed.[165] This approach may facilitate further assessment, monitoring and shared decision-making. Psychoeducation and lifestyle advice is recommended for all people with depression of any severity. Psychoeducation alone can achieve remission for some people with less severe depression.[230]

For people with less severe depression who wish to consider treatment, guidelines typically recommend non-pharmacological therapies first line, based on the assessment that the risk:benefit ratio does not justify the use of pharmacotherapy for mild depression.[165] [197] Less intensive options such as guided self-help and group CBT or behavioural activation may be a reasonable initial option in this group.[165] However it is important to note that, as for all patients with depression, treatment is individualised, and there may be reasons to consider pharmacological treatment from the offset in this group in certain circumstances (e.g., when there is a history of severe depression, where there is a lack of access to psychological treatment, when the patient has a preference for pharmacotherapy, or when there is a history of a previous positive treatment response to pharmacotherapy).

Combination psychological therapy and pharmacotherapy offers no demonstrated short-term advantage in this group. However, continued psychological therapy with antidepressant management is an effective option when continued through both acute and ongoing phases of treatment.[173]

The initial choice of therapy should be guided by patient preference. Options include:

- Supportive interventions: self-help books, yoga, relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture[231] [232][233] [234][235][236] [237] [238] [239] [240] [241] [242]
- Computer-based treatment: CBT, PST, and stress management.[243] [244] [245] [246] [247] [248] [249] [250]
- Antidepressant treatment
- Psychological therapy: CBT, IPT, PST, or a mindfulness-based intervention[251] [252] [253]

Supportive interventions

- For some people who have milder symptoms, the degree of impairment or distress from these symptoms might not outweigh the stigma the person attaches to accepting any form of psychiatric treatment; for these people a focus directly on symptom management may be the optimal strategy.[254]
- Self-help books are popular and may have long-term benefits for some patients.[231]
- Yoga may have a beneficial effect on depressive disorders, but there are significant variations in interventions, reporting, and feasibility.[255]
- Other supportive interventions include relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture.[232] [233] [234] [235] [236][237] [238] [239] [240] [241] [242] [256] [257] [258][259] In people with depression, higher remission rates were observed in a higher-dose exercise group plus continuation of SSRI treatment compared with low-dose exercise plus SSRIs.[238] Conversely, cessation of exercise may worsen depressive symptoms.[260] [261]

Computer-based treatment

- Internet- and mobile-based interventions are a promising and rapidly emerging development, and demonstrate efficacy. Digital interventions have the potential to widen access to evidence-based care for depression by reaching underserved populations, and may also increase the quality of care by augmenting face-to-face treatment. They may facilitate collaborative care, and shared decision-making.[243] [244] [245] [246] [247] [248] [249][250]
- They may be useful for people who cannot access or afford or schedule individual or group face-to-face CBT.
- The evidence is greatest for internet CBT (iCBT), and suggests that guided iCBT (iCBT supported by human guidance) is as effective as face-to-face CBT.[262] [263] Unguided CBT also demonstrates efficacy, but with smaller treatment effect sizes.[244] There may be an increasing role for other types of self-help and self-guided interventions such as behavioural activation strategies, particularly for those with less severe symptoms of depression.[250] [264] [265][266]
- Smartphone-based iCBT and novel app-based approaches are increasingly popular with patients; evidence of efficacy has not been established, although preliminary evidence as to their feasibility and efficacy looks promising.[267]
- Several key barriers to digital interventions have been noted, including concerns about reduced access to care for people with lower levels of digital literacy, which may include older people. There is evidence to suggest that 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.[268]

Psychological therapy

- Psychological therapy (CBT, IPT, or PST) is also considered a first-line option in less severe depression. Psychological therapy appears to have a positive impact on the quality of life of people with depression, beyond measurable reductions in depressive symptom severity.[269] As a general guide, the psychological interventions listed above in the section on ‘more severe depression’ are also suitable for people with ‘less severe depression'.[165] UK-based guidance from NICE also lists mindfulness-based therapy as a potential additional option in this group.[165] [270]
- Less severe depression treated with psychological therapy may be less likely to progress to more severe depression.[271]

Antidepressant treatment

- The routine use of antidepressants for patients with mild depression has been questioned based on weaker evidence for efficacy in people with milder symptomatology.[272] Some analyses have not consistently determined that mild depression responds less well to antidepressants than severe depression, although the evidence on this is mixed overall; other studies suggest an increasing magnitude of benefit of antidepressants with higher levels of depressive symptomatology.[166] [273] [274] [275][276]
- In the absence of definitive evidence, clinicians should therefore be guided by patient preference or other patient-specific factors in deciding whether to offer pharmacotherapy for less severe depression.
- If antidepressants are used, follow the same principles as for more severe depression (above).

Depression unresponsive to initial therapy

Regardless of depression severity, if the response to first-line therapy is inadequate, initial steps include reassessing the diagnosis, evaluating comorbidities, and exploring adherence to treatment.[277]

For those receiving antidepressants, continue treatment if there has been some improvement for at least the full 6-8 weeks. If the response is still incomplete, and if the drug is well-tolerated, and not already above the threshold of safe dose, consider increasing the dose. 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.[278]

Augmentation with psychological therapy is a good option to consider if there is a partial improvement with first-line pharmacotherapy, given that the evidence suggests that combined therapy works better than either treatment alone, with a synergistic effect of using both.[173] [174] [197] Switching from pharmacotherapy to a psychological therapy may be another reasonable option to consider, particularly for those with less severe depression (e.g., if the patient expresses this as a preference and can access CBT).[197]

Another option to consider if an antidepressant has been prescribed is switching to an alternative antidepressant.[279] [280] Switching may be appropriate if no improvement in symptoms has occurred within the first 2 weeks of treatment; however, be aware that early response may be, but is not necessarily, a reliable indicator of continued response.[281] [282] [283] [284]

Switching between antidepressants within a class may be considered initially (e.g., from one SSRI to another SSRI).[181] Next consider a change in drug class; for example, if a patient was on an SSRI, then consider an SNRI.[181] If treatment was not tolerated due to adverse effects, retry with an agent with fewer or different adverse effects. If an agent is switched, resume weekly follow-up until a response is apparent.

Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse.

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

Treatment-resistant/refractory depression

Evidence to guide treatment decisions when people with depression do not respond to initial treatments is very limited.[285] [286] The majority of patients with depression do not reach full remission after their first antidepressant trial, but a substantial proportion of those will respond to a second or third antidepressant.[280] The terms 'treatment-refractory' or 'treatment-resistant' depression have been used variously, and somewhat inconsistently, to denote depressive illness that has not remitted after two antidepressant trials of adequate dose and duration.[287] [288] An alternative term has been proposed to emphasise less the binary response of remission or non-remission and more the common scenario of partial, or inconsistent, treatment response: 'difficult-to-treat depression'.[289] Regardless of the terminology, guidelines typically suggest that clinicians working in primary care should request input from a psychiatrist after two unsuccessful treatment interventions; however, in practice this may need to be balanced against barriers to referral such as lack of specialist access.[182][290] Comorbid medical conditions, and psychosocial factors such as temperamental vulnerabilities, behaviour patterns, and life circumstances, may all make depression more difficult to treat.

New symptoms, attributed to medication side effects, commonly interrupt pharmacotherapy attempts; however, somatic symptoms are a common correlate of depressive disorder. Many perceived medication side effects, such as cognitive impairment, weight gain, and headache, occur just as frequently in study patients taking placebo.[291]

Reassessment

Reassessment can be useful after an apparently failed course of treatment, because some of the residual symptoms of depression (e.g., social avoidance, sleep/wake reversal, feelings of hopelessness) can reflect behavioural adaptations to depression, rather than depression itself. In such cases, symptoms may best be ameliorated through behavioural intervention or psychological therapy rather than a new medication trial. Cognitive deficits after remission of symptoms are common.[292] These may warrant monitoring and, if appropriate, the patient may benefit from reassurance that there may be continued improvement over time.

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.

Psychological treatment

- Check and ensure that the patient has started psychological therapy if multiple pharmacological agents have been unsuccessful; in particular, CBT appears to be effective at reducing symptoms in treatment-resistant depression with long-lasting results (up to at least 1 year).[293]

Antidepressant treatment

- Switching antidepressants: 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 (e.g., bupropion, mirtazapine, vilazodone, vortioxetine). One caveat about this approach, however, is that there are little high-quality clinical trials data to support switching antidepressants as opposed to continuing with the first (and raising the dose or trying augmentation strategies).[285]
- Combining antidepressants: the process of switching antidepressants, if undertaken, provides a window of opportunity for combined antidepressant therapy (i.e., an SSRI or SNRI plus bupropion

or mirtazapine) while crossing over from one to the other. However, there are little data to support the efficacy of antidepressant combinations.[294] [295] [296] [297] One notable exception to these observations is an apparently synergistic effect when the second antidepressant adds presynaptic alpha-2 receptor antagonism (e.g., mirtazapine, trazodone); however, as in other combination strategies, patient retention in treatment drops when additional drugs are added.[298] A specialist may prescribe two (or in rare cases more) antidepressants 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). There is some evidence that failure on one or several antidepressants does not preclude later success.[279] [280] 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.[282]

- Choice of alternative antidepressants: 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. UK guidance states that TCAs should only be prescribed for depression by a specialist clinician (e.g., psychiatrist) working in secondary care.[165]
- Monoamine oxidase inhibitors (MAOIs): in cases where nothing else has worked and the patient can tolerate a washout period from their current antidepressant, an 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.[299] [300] The washout period depends on the half-life of the antidepressant the patient is currently on and can range from 1-5 weeks. Do not use an MAOI without consulting a psychiatrist first.[165]
- Lithium augmentation: some studies show that combinations of antidepressants with other classes of medication are better than just a combination of different antidepressants alone.[301] In patients who have not responded to conventional antidepressants, lithium augmentation is an evidence-based approach.[302] [303] Lithium augmentation is initiated by a psychiatrist because of its narrow therapeutic index and risks of inadvertent toxicity from excessive dosing and drug-drug interactions.
- Antipsychotic augmentation: augmentation with some agents is becoming more common practice and may improve outcomes, including in older adults.[303] [304] [305] [306] However, intolerability and treatment discontinuation are more common with the majority of adjunctive antipsychotics compared to with placebo.[307] One cohort study reported increased mortality risk in patients receiving augmentation with an antipsychotic for depression compared with patients receiving augmentation with a second antidepressant.[308] It is unclear whether this is a pharmacological effect of antipsychotics or a reflection of the likelihood that antipsychotics tend to be prescribed to patients who are at higher risk for mortality for other reasons. Because of this potential risk, augmentation with an antipsychotic for treatment-resistant depression should typically be overseen by a psychiatrist who can determine the clinical necessity of choosing it over other strategies. Evidence better supports short-term versus long-term use of adjunctive antipsychotics.[309] Long-term use exposes patients to common antipsychotic side effects such as weight gain, akathisia, and, rarely, tardive dyskinesia. This concern applies as well to new agents such as brexpiprazole, which are similar to antipsychotics structurally but are marketed specifically for use in treatment-

resistant depression. Although deemed effective (in a small number of studies), the side effects are similar to other antipsychotics, and so it is important to consider whether benefits outweigh risks in people without psychosis.[310] [311] [312] [313] [314] [315]

- Esketamine nasal spray: may be considered by a consultant either as monotherapy or as an augmentation strategy (to be used with an oral antidepressant) for treatment-resistant depression. Although esketamine is being used more frequently in clinical practice, questions remain about which patients respond best to it, how long therapeutical effects might persist, and over what duration to continue treatment. While no longer considered a last-resort treatment, esketamine is not a first- or second-line treatment. A key practical consideration is the logistical and occupational commitments required of patients; for example, the need to take time away from work and to arrange necessary transport and support. Availability of esketamine varies according to country of practice and relevant regulatory approval. In the US, the drug is only available through a restricted distribution programme. 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, respiratory depression, 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. Esketamine is contraindicated in patients with aneurysmal vascular disease, arteriovenous malformation, or intracerebral haemorrhage. Use of esketamine nasal spray beyond 4 weeks is not currently supported by evidence, given that its effectiveness beyond 4 weeks has not yet been evaluated.
- Other augmentation strategies may be used by specialists (e.g., thyroid hormone, pindolol, and modafinil, as well as emerging treatments such as ketamine and transcranial magnetic stimulation).[316] [317] [318]

ECT

- 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 patients with milder depression. 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. Combined with antidepressants, lithium has been shown to reduce the risk for relapse post-ECT.[319]

Duration of pharmacological treatment

Duration of antidepressant treatment following the remission of symptoms depends on the prior course of illness. Data on treatment outcomes beyond the initial weeks of treatment are limited, although one systematic review suggests that the efficacy of antidepressants compared with placebo is stable over at least the first 6 months of treatment.[320] In general, there appears to be a reduced risk of relapse when antidepressants are continued for 6 months or over.[321] [322] [323]

Based on this, it is advisable to continue successful antidepressant treatment for at least 6-12 months following remission.[165] [322]

For people prescribed an antipsychotic for depression with psychotic symptoms, UK guidance recommends continuing antipsychotic treatment for a number of months after remission, if tolerated.

NICE recommends that the decision about if and when to stop an antipsychotic should be made by, or in consultation with, specialist psychiatric services.[165]

Discontinuation of antidepressant treatment has consistently been associated with a greater risk of relapse than does continuing treatment, and is therefore a complex clinical decision.[324] [325] [326] While the risk of relapse over a population of patients increases off treatment, a substantial proportion of patients may stop antidepressants without consequence.[327] For some people at increased risk of relapse, continuation of treatment beyond this period may be considered. Shared decision-making is recommended. See Maintenance treatment and relapse prevention.

Discontinuation of medication for depression

The most immediate concern when removing a patient from antidepressant treatment is the possibility of rapid relapse, if in fact the antidepressant was still serving its purpose. Beyond that, some antidepressants, particularly those in the SSRI or SNRI classes, are associated with a 'discontinuation syndrome'. Typical are flu-like symptoms, hyperarousal, insomnia, vertigo, and sensory disturbances (e.g., 'brain zaps'). Patients will often know how vulnerable they are to these symptoms, if they have ever skipped a dose or run out of their medication. Clinicians should slowly decrease the dose to reduce the risk of unpleasant discontinuation symptoms; this can usually be done over several weeks, but in some cases may take several months or longer in particularly susceptible patients.[324] [328] Drugs with shorter half-lives (e.g., paroxetine, venlafaxine) may require longer periods of taper.[329] A proportionate method of tapering is recommended by some treatment guidelines; this involves reductions as a proportion of the previous dose (e.g., 25%) rather than reducing the dose by a fixed increment each time.[165] If the required dose is not available in tablet form, a liquid preparation may be required (if available). Be aware that people's experiences of discontinuation symptoms can vary substantially from mild and transient to longer-lasting and more severe. Anticipatory discussion with the patient is important, including when and how to seek support from a healthcare professional in the event of such symptoms.[329] Closely monitor the patient to ensure that any apparent emerging discontinuation symptoms do not in fact represent a relapse of their depression.[272] [330]

UK guidance advises that antipsychotics for psychotic depression should only be stopped in specialist mental health services, or following specialist mental health advice. When stopping an antipsychotic, reduce the dose gradually over at least 4 weeks, and in proportion to the length of treatment.[165]

Maintenance treatment and relapse prevention

For patients established on antidepressants, regularly review their antidepressant use to assess efficacy and the presence of any adverse effects, and to ensure that long-term use remains clinically indicated.[272]

Shared decision-making is recommended; options for those already taking an antidepressant who have achieved full or partial remission are:[165]

- Continuing antidepressant treatment
- Switching to a psychological treatment for relapse prevention
- Continuing with the same antidepressant and adding on a psychological treatment for relapse prevention.

Maintenance on antidepressants following remission does not guarantee protection from relapse, but there is evidence of at least a modest benefit.[331]

The World Federation of Societies of Biological Psychiatry (WFSBP) supports the use of maintenance treatment for recurrent depression in some circumstances; WFSBP recommends maintenance treatment for 5-10 years, or indefinitely, for those people at greater risk of recurrent depression, particularly when two or three attempts to withdraw pharmacotherapy have been followed by another episode within a year.[332]

The selection and success of treatment for relapse prevention depends on the type and severity of depressive symptoms, but most often relies on trial and error.

There is a growing body of evidence supporting the use of psychological therapy for prevention of relapse and recurrence, both when used alone and in combination with pharmacotherapy.[175] [333] Specific modalities with demonstrated efficacy for relapse prevention include preventive CBT, mindfulness-based CBT, and interpersonal therapy (IPT).[165] [334] 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.[335] [336] [337] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[338] There is evidence that switching in the maintenance phase from pharmacotherapy to psychotherapy can be at least as effective in preventing relapse as staying with pharmacotherapy.[333] [339] Psychological therapy 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.

Recurrent episodes

Recurrent episodes of major depression should be treated with the same antidepressant that previously induced remission, provided that the recurrences do not occur while under adequate maintenance treatment with such medication.

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. Studies of the safety of antidepressant use in pregnancy for the most part add up to minimal risk to the fetus.[340] [341] There is little controlled trial evidence. Consistent data to support fully informed decision-making are lacking.

Obstetric risks of antidepressant use during pregnancy

Cohort studies have reported a small increased risk of pre-eclampsia, postnatal haemorrhage, and gestational diabetes in women who continue antidepressants throughout pregnancy.[342] [343] Based on mixed evidence for an increased risk of postnatal haemorrhage associated with antidepressants, the UK government has advised caution.[344]

Psychiatric risks of antidepressant discontinuation

Women who stop their antidepressant are more likely to have a relapse of depression during their pregnancy.[345] [346] UK national enquiry data show that in women in contact with UK psychiatric services, peinatal suicides are more likely to occur in those with a depression diagnosis and no active treatment at the time of death.[347]

Effects on the fetus and child

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.[348]

For infants exposed to antidepressants during pregnancy, evidence as to whether there is an increased risk of preterm birth and low birth weight compared to infants of mothers with untreated depression is mixed.[343] [349] [350] [351] [352] [353] [354]

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.[355]

There is a small increased risk of persistent pulmonary hypertension of the newborn with maternal SSRI and SNRI use in any trimester (number needed to harm = 100).[356] [357]

Recommendations for management

Clinicians and patients should 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. In the US, such discussions are frequently carried out by the patient's obstetrician; obstetricians in the US may seek further consultant treatment advice from Perinatal Psychiatry Access Programs where available.[358] In other locations (e.g., the UK) clinicians should consult a consultant with experience in perinatal mental health as part of this process. The American College of Obstetricians and Gynecologists (ACOG) recommends that if pharmacological treatment is required for perinatal depression, SSRIs may be used as first-line pharmacotherapy, and SNRIs are reasonable alternatives.[358] Despite the lack of consistent evidence of harmful effects of antidepressants to fetal and infant health and development, caution is required.

Some classes of antidepressants, such as TCAs and MAOIs, are not routinely used for depression in pregnancy, owing to concerns about potential risks to the mother and baby.[358] Esketamine nasal spray is a relatively new drug and is not recommended in pregnancy, as studies involving pregnant animals treated with ketamine indicate that esketamine may cause harm to the fetus when used during pregnancy.

Updated information about potential harms from antidepressants and other pharmaceuticals can be found at various resources. [UK Teratology Information Service] (http://www.uktis.org)

Severity of depressive symptoms may influence treatment choice. For women with very severe major depression in pregnancy, ECT may be the treatment of choice as it does not expose the fetus to any known risk.[359] [360] For more severe depression, the risk to the fetus from the potentially harmful effects of the mother's untreated depression on her health might outweigh any detectable risk to the fetus from antidepressants.[340] [341] [361] Where the maternal and fetal risk of untreated depression is low, as in mild to moderate depression, the risk/benefit balance may tip in favour of non-pharmacological therapies, as reflected in several treatment guidelines worldwide.[358] [362]

Psychological treatments have essentially no risk of side effects and may be offered as one first-line option for depression occurring in pregnancy, particularly for those with less severe depression.[358] 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.[363] [364]

It is important to consider and address any coexisting psychosocial problems, such as intimate partner violence.

Postnatal depression

See Postnatal depression .

Older adults with depression (age >65 years)

The treatment of depression in older adults is broadly similar to that in younger adult patients, and antidepressants are an effective treatment for depression in this group.[11] Collaborative care models may be particularly useful for this patient group.[365] [366] There is evidence of efficacy for psychological treatments for older people with depression, including older adults residing in long-term care settings, although the evidence is uncertain.[367] Suicide risk mitigation is an important consideration, given the relatively higher rates of suicidal ideation in this age-group.[368]

Caution is required when prescribing for older patients with depression (as with any pharmacological treatment in older people) due to an increased risk of side effects and increased use of concurrent medication in this population. Clinicians should typically start at the lowest dose and titrate up slowly when prescribing any drug treatment in older adults, and be aware of potential drug interactions. However, if older adults are unresponsive to a low dose of antidepressants, a higher dose may be required; many older patients ultimately require the same doses of antidepressant that are used for younger adults.

The Screening Tool of Older Persons Prescriptions and Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria is a reliable screening tool enabling prescribers to avoid potentially inappropriate treatment (and under-treatment) in adults over the age of 65 years.[11] [STOPP-START] (https://www.cgakit.com/m-2-stopp-start)

ECT may be a suitable treatment for older patients with severe depression and avoids complications arising from drug-related adverse effects.[178]

Comorbidities

Antidepressants may be effective in reducing depression and alcohol consumption in patients with comorbid depression and alcohol dependence.[369] Antidepressant use in depressed patients who are on opioid agonist therapy is not well supported.[370] 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.[371] There is some evidence for CBT-based treatments added to usual care in this patient group.[372] Evidence from one Cochrane review concluded that CBT-based treatments added to usual care probably have a small positive effect on symptoms of depression and quality of life when added to usual care for people with dementia and mild cognitive impairment.[372] One large-scale meta-analysis concluded that psychological interventions may be superior to pharmacological treatment in patients with dementia.[373] Evidence is also low quality, but more favourable, for antidepressants in patients with depression and HIV infection.[374] Support for antidepressants for depression comorbid with cancer is mixed.[155] [375] Non-pharmacological approaches for the management of depressive symptoms both during and after cancer treatment (e.g., mindfulness-based interventions, yoga, music therapy, relaxation, reflexology and tai chi, and/or qigong) have been recommended according to integrative oncology treatment guidelines.[376]

Treatment algorithm overview

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

Acute (summary)		
at risk of harm to self or others (psychotic, suicidal, severe psychomotor retardation impeding activities of daily living, catatonia, or severe agitation): non-pregnant		
	1st	**urgent psychiatric referral ± hospitalisation**
	plus	**antidepressant**
	adjunct	**immediate symptom management with benzodiazepine ± antipsychotic**
	adjunct	**esketamine nasal spray**
	adjunct	**electroconvulsive therapy (ECT)**
	2nd	**increase dose or switch to alternative antidepressant**
at risk of harm to self or others (psychotic, suicidal, severe psychomotor retardation impeding activities of daily living, catatonia, or severe agitation): pregnant		
	1st	**urgent psychiatric referral ± hospitalisation (with psychiatric and obstetric involvement)**
more severe depression (PHQ score ≥16): non-pregnant		
	1st	**antidepressant and/or psychological therapy**
	plus	**psychoeducation and lifestyle advice**
	adjunct	**immediate symptom management with benzodiazepine ± antipsychotic**
	adjunct	**esketamine nasal spray**
	adjunct	**electroconvulsive therapy (ECT)**
	2nd	**increase antidepressant dose or switch to alternative treatment or combination therapy**
	plus	**psychoeducation and lifestyle advice**
	adjunct	**esketamine nasal spray**
	adjunct	**electroconvulsive therapy (ECT)**

Acute (summary)		
less severe depression (PHQ <16): non-pregnant		
	1st	active monitoring
	plus	psychoeducation and lifestyle advice
	1st	supportive interventions
	plus	psychoeducation and lifestyle advice
	1st	computer-based interventions
	plus	psychoeducation and lifestyle advice
	1st	psychological therapy
	plus	psychoeducation and lifestyle advice
	1st	antidepressant
	plus	psychoeducation and lifestyle advice
	2nd	increase antidepressant dose or switch to alternative treatment
	plus	psychoeducation and lifestyle advice
treatment-resistant/refractory depression		
	1st	reassess and switch to alternative antidepressant or combination therapy
	plus	consider augmentation pharmacotherapy
	plus	psychological therapy or other non-pharmacological treatment
	plus	psychoeducation and lifestyle advice
	2nd	electroconvulsive therapy (ECT)
	plus	psychological therapy or other non-pharmacological treatment
	plus	psychoeducation and lifestyle advice
pregnant		
	1st	active monitoring and/or antidepressant and/or electroconvulsive therapy (ECT)
	plus	psychological therapy
	plus	psychoeducation and lifestyle advice

Ongoing		(summary)
treatment responsive		
	1st	**maintenance antidepressant and/or psychological therapy**
	plus	**psychoeducation and lifestyle advice**
recurrent episode		
	1st	**repeat of remission-inducing regimen or long-term therapy**
	plus	**psychoeducation and lifestyle advice**

Treatment algorithm

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

at risk of harm to self or others (psychotic, suicidal, severe psychomotor retardation impeding activities of daily living, catatonia, or severe agitation): non-pregnant

1st **urgent psychiatric referral ± hospitalisation**

» These people are at increased risk for suicide, impulsive and potentially self-destructive behaviour, and health complications due to poor self-care and immobility.

» Refer urgently to a psychiatrist. Suicide risk mitigation is critical. Consider hospitalisation for people: with significant suicidal ideation or intent who lack adequate safeguards in their family environment; with intent to hurt others; who are unable to care for themselves and adhere to their treatment; who have psychotic symptoms, or uncontrolled agitation accompanied by the risk of impulsive behaviour.[165] [181] [182] If the individual is unwilling to be hospitalised, engage family support and, if necessary, exercise legal means to compel treatment.

» Specialist referral, hospitalisation, constant observation, tranquilisation, and/or electroconvulsive therapy may be required to ensure safety until definitive antidepressant therapy can take effect.

» People with agitation 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 people 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 people may require supportive nursing care.

plus **antidepressant**

Treatment recommended for ALL patients in selected patient group

Primary options

Acute

» 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

» levomilnacipran: 20 mg orally once daily initially for 2 days, increase to 40 mg once

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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

» Antidepressant therapy is usually the first-line option in most patients. Electroconvulsive therapy (ECT) is the first-line treatment in some people with severe depression, but when immediate ECT is either not indicated or not an option, antidepressant pharmacotherapy is crucial.

» US guidance recommends that initial pharmacological treatment should be with a second-generation antidepressant. This may include a selective serotonin-reuptake

Acute

inhibitor (SSRI; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline); a serotonin-noradrenaline reuptake inhibitor (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).[197] UK guidance recommends offering an SSRI as first-line treatment for most people with depression for whom pharmacological treatment is suitable.[165] SNRIs are recommended by NICE as a later-line option.[165] According to UK guidance, clinicians should only consider prescribing vortioxetine when there has been no or limited response to at least 2 previous antidepressants.[165]

» No consistent differences in safety or efficacy have been demonstrated between antidepressants.[202] [203] While a few meta-analyses of comparative treatment efficacy have favoured one drug over others, by and large they are comparable in efficacy.[204] [205]

» Choice of drug should be based on patient preference, tolerability, and past evidence of effectiveness in the patient.[181]

» Depressed patients with undiagnosed bipolar affective disorder may convert to frank mania if they receive antidepressants. Ask patients about a prior history of manic episodes (e.g., periods of days to weeks marked by unusually high energy, euphoria, insomnia, hyperactivity, or impaired judgment) before starting antidepressant therapy.

» There is some evidence of increased suicidal thoughts and behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[210] [211] [212] [213] This association is not necessarily causal and may instead be attributable to confounding factors.[214] Close monitoring and risk management is recommended when prescribing an antidepressant to a person under the age of 25 years, or to anybody thought to be at increased risk for suicide.[165]

» 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. Titrate

Acute

the antidepressant dose to the maximum tolerated in patients who experience a partial response after 2-4 weeks. Patients may begin to show a response within the first 1-2 weeks of treatment; however, one fifth of those who have not previously responded may begin to respond after week 5.[216] Successful antidepressant therapy to the point of remission of all symptoms may be expected to 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 6-12 months following remission, before considering discontinuation.[165] [322] However, some treatment guidelines recommend that patients with frequent recurrences and relapses, who respond successfully to antidepressant treatment, may require longer-term or indefinite pharmacological therapy, following shared decision-making.[332]

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

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

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» quetiapine: consult specialist for guidance on dose

OR

» fluphenazine: consult specialist for guidance on dose

OR

» trazodone: consult specialist for guidance on dose

» 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. Short-term 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.[186]

» 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 patients with severe depression under several circumstances. Antidepressants alone may not effectively address psychotic symptoms, such as delusions or hallucinations.[184]

» People with catatonia can be treated with a benzodiazepine (e.g., lorazepam, clonazepam), sometimes in combination with an antipsychotic and ECT.[187] 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

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maximum dose or leads to intolerable adverse effects at lower doses, switch to another agent.

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

adjunct **esketamine nasal spray**

Treatment recommended for SOME patients in selected patient group

Primary options

» esketamine nasal: (28 mg/device) 84 mg intranasally twice weekly for 4 weeks, may decrease dose to 56 mg twice weekly based on tolerability
Use in conjunction with an oral antidepressant for this indication. Evaluate benefit after 4 weeks before continuing treatment; use beyond 4 weeks has not been evaluated for this indication. Each device contains 2 sprays (1 spray for each nostril) and delivers a total of 28 mg per device. Use of 2 or 3 devices is required to achieve the recommended dose. A 5-minute rest between the use of devices is recommended.

» Esketamine (an active isomer of ketamine, an N-methyl-D-aspartate [NMDA] receptor antagonist) may be considered by a consultant for depression with acute suicidal ideation or behaviour, as an adjunct to an oral antidepressant.

» Although esketamine is being used more frequently in clinical practice, questions remain about which patients respond best to it, how long therapeutical effects might persist, and over what duration to continue treatment. While no longer considered a last resort treatment, esketamine is not a first- or second-line treatment.

» Availability of esketamine varies according to country of practice and relevant regulatory approval. In the US, the drug is only available through a restricted distribution programme.

» 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, respiratory depression, difficulty with attention, judgement and thinking

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(dissociation), suicidal thoughts and behaviours, and the potential for drug misuse. Monitor respiratory status and blood pressure during treatment.

» 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. Esketamine is contraindicated in patients with aneurysmal vascular disease, arteriovenous malformation, or intracerebral haemorrhage.

» Use of esketamine nasal spray beyond 4 weeks is not currently supported by evidence, given that its effectiveness beyond 4 weeks has not yet been evaluated.

adjunct **electroconvulsive therapy (ECT)**

Treatment recommended for SOME patients in selected patient group

» In certain patients with severe depression who have psychotic features, active suicidal thoughts, catotonia or who are unresponsive to or intolerant of antidepressants, or who have had a previous positive response to ECT, ECT may be considered early in the course of treatment.[39] [177] ECT is often the treatment of choice for severely depressed older patients because it is effective, and avoids the complications that may arise from pharmacological intolerance and drug interactions associated with treatment for comorbid physical conditions.[178]

» ECT is performed under general anaesthesia, typically 2 or 3 times a week for a total of 6-12 treatments.[188]

» Patient and clinician must be fully informed of the potential risks, including the risks associated with not having ECT, so that the patient can provide informed consent.[165] The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments, meaning that it is one of the safer procedures performed under general anaesthetic.[189] [190] Overall, there is no increase in risk of medical complications in patients receiving ECT versus equally depressed patients not receiving ECT.[191] ECT affects heart rate and blood pressure. Chest pain, arrhythmias, persistent hypertension, and ECG changes have been reported as complications, particularly in patients with pre-existing cardiac disease.[192] Cardiovascular conditions should be stabilised before administering ECT.[192] The majority of patients report adverse cognitive effects during and shortly after treatment, most

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commonly memory loss (both anterograde and retrograde amnesia).[194] This impairment seems to be short-lived according to objective assessment, although a significant proportion of patients report persistent memory loss following ECT.[193] [194] This potential risk must be balanced against the evidence in favour of its efficacy, especially in patients with severe depression. If a person with depression cannot give informed consent for ECT, it should only be given when it does not conflict with a valid advance treatment decision made by the person.[165]

» ECT treatment effects are temporary; following successful treatment, the effect must be maintained by the use of antidepressants and/or maintenance electroconvulsive treatments (typically once per week to once every 4 weeks or longer, titrated to stability).[195] Combined with antidepressants, lithium has been shown to reduce the risk for relapse post-ECT.[319]

2nd **increase dose or switch to alternative antidepressant**

» If the response to first-line therapy is inadequate, initial steps include reassessing the diagnosis, evaluating comorbidities, and exploring adherence to treatment.[277]

» Continue treatment if there has been some improvement for at least the full 6-8 weeks. If the response is still incomplete, and if the drug is well-tolerated, and not already above the threshold of safe dose, consider increasing the dose. 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.[278]

» Another option to consider is switching to an alternative antidepressant.[279] [280] 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.[281] [282] However, early response may be, but is not necessarily, a reliable indicator of continued response.[283] [284]

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

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inhibitor. If treatment was not tolerated due to adverse effects, retry with an agent with fewer or different adverse effects. If an agent is switched, resume weekly follow-up until a response is apparent.

» Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse.

» The timeframe required for safely switching depends on various factors, including the pharmacokinetic properties of the drugs and possible interactions between them, as well as patient characteristics such as age, sensitivity to adverse effects, and the capacity to wait to begin a new course of treatment. In some situations, it is possible to give both drugs for a short period of time while the changeover is occurring; however, this should only be done under specialist guidance. In other cases, it is safer to take a more conservative approach. This involves slowly tapering the dose of the first drug before stopping it, and then waiting a period of time before starting the second drug (known as a washout period, which is usually five half-lives of the first drug). Drugs with longer half-lives (e.g., fluoxetine) require longer washout periods (e.g., up to 5-6 weeks) when combined with a drug with which the combination is contraindicated (e.g., monoamine oxidase inhibitors with fluoxetine). Specific recommendations for switching from one antidepressant to another, along with suitable washout periods, are available and local guidance should be consulted. When in doubt, 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 6-12 months following remission, before considering discontinuation.[165][322] However, some treatment guidelines recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require longer-term or indefinite pharmacological indefinite therapy, following shared decision-making.[332]

» 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.

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at risk of harm to self or others (psychotic, suicidal, severe psychomotor retardation impeding activities of daily living, catatonia, or severe agitation): pregnant

1st **urgent psychiatric referral ± hospitalisation (with psychiatric and obstetric involvement)**

» These people are at increased risk for suicide, impulsive and potentially self-destructive behaviour, and health complications due to poor self-care and immobility.

» Refer urgently to a psychiatrist; joint psychiatric and obstetric involvement is required to ensure the safety of both mother and fetus. Suicide risk mitigation is critical. Consider hospitalisation for people: with significant suicidal ideation or intent who lack adequate safeguards in their family environment; with intent to hurt others; who are unable to care for themselves and adhere to their treatment; who have psychotic symptoms, or uncontrolled agitation accompanied by the risk of impulsive behaviour.[165] [181] [182] If the individual is unwilling to be hospitalised, engage family support and, if necessary, exercise legal means to compel treatment.

» Specialist referral, hospitalisation, constant observation, and/or electroconvulsive therapy (ECT) may be required to ensure safety until definitive antidepressant therapy can take effect.

» People with agitation 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 people 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 people may require supportive nursing care.

» Severity of depressive symptoms may influence treatment choice. In very severe depression in pregnancy, ECT may the treatment of choice when the severity of illness puts the patient and/or fetus at risk either due to poor maternal self-care or suicide. There is no known risk to the fetus from ECT.[359] [360]

» Antidepressants may be considered, following shared decision-making based on individualised

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risk:benefit assessment: In the US, such discussions are frequently carried out by an obstetrician; obstetricians in the US may seek further specialist treatment advice from Perinatal Psychiatry Access Programs where available.[358] In other locations (e.g., the UK) input from a specialist with experience in perinatal mental health is typically required. The American College of Obstetricians and Gynecologists (ACOG) recommends that if pharmacological treatment is required for perinatal depression, selective serotonin-reuptake inhibitors (SSRIs) may be used as first-line pharmacotherapy, and serotonin-noradrenaline reuptake inhibitors (SNRIs) are reasonable alternatives.[358] Despite the lack of consistent evidence of harmful effects of antidepressants to fetal and infant health and development, caution is required.

» Some classes of antidepressants, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), are not routinely used for depression in pregnancy, owing to concerns about potential risks to the mother and baby.[358] Esketamine nasal spray is a relatively new drug and is not recommended in pregnancy, as studies involving pregnant animals treated with ketamine indicate that esketamine may cause harm to the fetus when used during pregnancy.

» Updated information about potential harms from antidepressants and other pharmaceuticals can be found at various resources. [UK Teratology Information Service] (http://www.uktis.org)

more severe depression (PHQ score ≥16): non-pregnant

1st

antidepressant and/or psychological therapy

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

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» 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, increase gradually according to response, maximum 225 mg/day

Acute

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

» More severe depression has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of 16 or more.[165] This category includes both moderate and severe depression, as defined by DSM-5-TR.[165]

» Treatment decisions are informed by a number of important real-world considerations, including access to psychological treatment, which may be limited or non-existent in some locations. Furthermore, people with depression may have a strong preference for psychological therapy or pharmacotherapy. Research to guide evidence-based individualised treatment is at an early stage.[179] Choice of treatment is therefore highly individualised and empirically validated.

» Treatment options for more severe depression include pharmacotherapy and psychological therapy, either alone or in combination.[165] [197] Both pharmacotherapy and psychological therapy have shown effectiveness when used alone, and yield similar results in randomised trials.

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» Results from one meta-analysis of antidepressant treatment for adults with depression suggest numbers needed to treat (NNT) values of 16, 11, and 4 for the mild-to-moderate, severe, and very-severe subgroups, respectively.[166]

» Although monotherapy with a psychological therapy is one potential option as endorsed by some treatment guidelines, the author notes that evidence to support this approach is limited.[165] [197] [198] [199] In the absence of definitive evidence supporting psychological treatment as monotherapy for more severe depression, clinicians should consider patient preferences or other individual factors to guide this decision. A stepped care model may be considered, whereby those who do not respond adequately to psychological treatment alone are offered timely add-on pharmacological treatment.[198]

» The World Health Organization (WHO) recommends that psychological interventions are included within the treatment regimen whenever possible for all adults with moderate-to-severe depression.[198]

» The combination of psychological therapy plus pharmacotherapy has been demonstrated to be more effective than either treatment alone for those with more severe depression.[171] [172] [173] [174] Furthermore, the addition of psychological therapy to the treatment regimen is associated with a more enduring treatment effect than when pharmacotherapy is used alone.[169] [175][377]

» Psychological treatments may be delivered via different methods and settings, and may include individual, group, or virtual sessions. No clear differences in efficacy have been found among different types of psychological therapies used for depression.[217]

» Published treatment guidelines recommend a range of psychological therapies as first-line options more severe depression, including cognitive behavioural therapy, behavioural activation, short-term psychodynamic therapy, interpersonal psychotherapy, and problem-solving therapy.[165] [218] However guidance from the American College of Physicians only recommends CBT, citing insufficient evidence to support other types of psychological therapies.[197]

» Cognitive behavioural therapy (CBT) has shown greater efficacy than pharmacological

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placebo across levels of severity.[219] Treatment response to CBT is comparable with antidepressant response in some studies.[170] [Evidence B] 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.[175] [335] [336] [337]

» US guidance recommends that initial pharmacological treatment should be with a second-generation antidepressant. This may include a selective serotonin-reuptake inhibitor (SSRI; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline); a serotonin-noradrenaline reuptake inhibitor (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).[197] UK guidance recommends offering an SSRI as first-line treatment for most people with depression for whom pharmacological treatment is suitable.[165] SNRIs are recommended by NICE as a later-line option.[165] According to UK guidance, clinicians should only consider prescribing vortioxetine when there has been no or limited response to at least 2 previous antidepressants.[165]

» No consistent differences in safety or efficacy have been demonstrated between antidepressants.[202] [203] While a few meta-analyses of comparative treatment efficacy have favoured one drug over others, by and large they are comparable in efficacy.[204] [205]

» Choice of drug should be based on patient preference, tolerability, safety in overdose, presence of other psychiatric illness, and past evidence of effectiveness in the patient.[181]

» Depressed patients with undiagnosed bipolar affective disorder may convert to frank mania if they receive antidepressants. 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.

» There is some evidence of increased suicidal thoughts and behaviour in the first weeks of treatment, particularly in teenagers and

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young adults, and in those on relatively high starting doses.[210] [211] [212] [213] This association is not necessarily causal and may instead be attributable to confounding factors.[214] Close monitoring and risk management is recommended when prescribing an antidepressant to a person under the age of 25 years, or to anybody thought to be at increased risk for suicide.[165]

» Follow up patients 1-2 weeks after initiating therapy, regardless of treatment type, 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.

» For people taking antidepressants, titrate the dose to the maximum tolerated in patients who experience a partial response after 2-4 weeks. Patients may begin to show a response within the first 1-2 weeks of treatment; however, one fifth of those who have not previously responded may begin to respond after week 5.[216] Successful antidepressant therapy to the point of remission of all symptoms may be expected to 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 6-12 months following remission, before considering discontinuation.[165] [322] However, some treatment guidelines recommend that patients with frequent recurrences and relapses, who respond successfully to antidepressant treatment, may require longer-term or indefinite pharmacological therapy, following shared decision-making.[332]

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

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them

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to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

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

» quetiapine: consult specialist for guidance on dose

OR

» trazodone: consult specialist for guidance on dose

» Patients with mild agitation or severe anxiety can be treated with the short-term use of a benzodiazepine (e.g., lorazepam, clonazepam) and/or an antipsychotic (e.g., quetiapine). However, one cohort study reported increased mortality risk in patients receiving augmentation with an antipsychotic for depression compared with patients receiving augmentation with a second antidepressant.[308] 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

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maximum dose or leads to intolerable adverse effects at lower doses, switch to another agent.

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

adjunct **esketamine nasal spray**

Treatment recommended for SOME patients in selected patient group

Primary options

» esketamine nasal: (28 mg/device) 84 mg intranasally twice weekly for 4 weeks, may decrease dose to 56 mg twice weekly based on tolerability
Use in conjunction with an oral antidepressant for this indication. Evaluate benefit after 4 weeks before continuing treatment; use beyond 4 weeks has not been evaluated for this indication. Each device contains 2 sprays (1 spray for each nostril) and delivers a total of 28 mg per device. Use of 2 or 3 devices is required to achieve the recommended dose. A 5-minute rest between the use of devices is recommended.

» Esketamine (an active isomer of ketamine, an N-methyl-D-aspartate [NMDA] receptor antagonist) may be considered by a consultant for depression with acute suicidal ideation or behaviour, as an adjunct to an oral antidepressant.

» Although esketamine is being used more frequently in clinical practice, questions remain about which patients respond best to it, how long therapeutical effects might persist, and over what duration to continue treatment. While no longer considered a last resort treatment, esketamine is not a first- or second-line treatment.

» Availability of esketamine varies according to country of practice and relevant regulatory approval. In the US, the drug is only available through a restricted distribution programme.

» 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, respiratory depression, difficulty with attention, judgement and thinking

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(dissociation), suicidal thoughts and behaviours, and the potential for drug misuse. Monitor respiratory status and blood pressure during treatment.

» 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. Esketamine is contraindicated in patients with aneurysmal vascular disease, arteriovenous malformation, or intracerebral haemorrhage.

» Use of esketamine nasal spray beyond 4 weeks is not currently supported by evidence, given that its effectiveness beyond 4 weeks has not yet been evaluated.

adjunct **electroconvulsive therapy (ECT)**

Treatment recommended for SOME patients in selected patient group

» Electroconvulsive therapy (ECT) may be an option for those who have not responded to, or cannot tolerate, antidepressants.[165] The response rate is better for patients with severe major depression than for moderate or mild depression.[177] The potential impact on memory and cognition, which may reduce functioning during active treatment, make ECT less desirable for patients with milder depression. ECT is often the treatment of choice for severely depressed people with late-life depression, because it is effective, and avoids complications that may arise from pharmacological intolerance and drug interactions associated with treatment for comorbid physical conditions.[178]

» ECT is performed under general anesthesia, typically 2 or 3 times a week for a total of 6-12 treatments.[188]

» Patient and clinician must be fully informed of the potential risks, including the risks associated with not having ECT, so that the patient can provide informed consent.[165] The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments, meaning that it is one of the safer procedures performed under general anesthetic.[189] [190] Overall, there is no increase in risk of medical complications in patients receiving ECT versus equally depressed patients not receiving ECT.[191] ECT affects heart rate and blood pressure. Chest pain, arrhythmias, persistent hypertension, and ECG changes have been reported as complications, particularly in patients with pre-existing cardiac

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disease.[192] Cardiovascular conditions should be stabilised before administering ECT.[192] The majority of patients report adverse cognitive effects during and shortly after treatment, most commonly memory loss (both anterograde and retrograde amnesia).[194] This impairment seems to be short-lived according to objective assessment, although a significant proportion of patients report persistent memory loss following ECT.[193] [194] This potential risk must be balanced against the evidence in favour of its efficacy, especially in patients with severe depression. If a person with depression cannot give informed consent for ECT, it should only be given when it does not conflict with a valid advance treatment decision made by the person.[165]

» ECT treatment effects are temporary; following successful treatment, the effect must be maintained by the use of antidepressants and/or maintenance electroconvulsive treatments (typically once per week to once every 4 weeks or longer, titrated to stability).[195] Combined with antidepressants, lithium has been shown to reduce the risk for relapse post-ECT.[319]

2nd **increase antidepressant dose or switch to alternative treatment or combination therapy**

» If the response to first-line therapy is inadequate, initial steps include reassessing the diagnosis, evaluating comorbidities, and exploring adherence to treatment.[277]

» For those already being treated with an antidepressant, continue treatment if there has been some improvement for at least the full 6-8 weeks. If the response is still incomplete, and if the drug is well-tolerated, and not already above the threshold of safe dose, consider increasing the dose. 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.[278]

» Augmentation with psychological therapy is a good option to consider if there is a partial improvement with first-line pharmacotherapy, given that the evidence suggests that combined therapy works better than either treatment alone owing to a synergistic effect of using both.[173] [174] [197] Likewise, patients who do not respond adequately to psychological

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treatment alone may be offered add-on pharmacological treatment.[198] Switching from pharmacotherapy to a psychological therapy, or from a pharmacological therapy to pharmacotherapy, may be another reasonable option to consider, as guided by patient preference and access to CBT.[197]

» Another option to consider for those already receiving pharmacotherapy is switching to an alternative antidepressant.[279] [280] Switching may be appropriate if no improvement in symptoms has occurred within the first 2 weeks of treatment.[281] [282] However, early response may be, but is not necessarily, a reliable indicator of continued response.[283] [284]

» Switching between antidepressants within a class may be considered initially (e.g., from one selective serotonin-reuptake inhibitor [SSRI] to another SSRI).[181] Next consider a change in drug class; for example, if a patient was on an SSRI, then consider a serotonin noradrenaline-reuptake inhibitor (SNRI).[181] If treatment was not tolerated due to adverse effects, retry with an agent with fewer or different adverse effects. If an agent is switched, resume weekly follow-up until a response is apparent.

» Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. See Serotonin syndrome .

» 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

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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 6-12 months following remission, before considering discontinuation.[165] [322] However, some physicians recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require longer-term or indefinite indefinite pharmacological therapy, following shared decision-making.[332]

» 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.

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

adjunct **esketamine nasal spray**

Treatment recommended for SOME patients in selected patient group

Primary options

» esketamine nasal: (28 mg/device) 84 mg intranasally twice weekly for 4 weeks, may

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decrease dose to 56 mg twice weekly based on tolerability
Use in conjunction with an oral antidepressant for this indication. Evaluate benefit after 4 weeks before continuing treatment; use beyond 4 weeks has not been evaluated for this indication. Each device contains 2 sprays (1 spray for each nostril) and delivers a total of 28 mg per device. Use of 2 or 3 devices is required to achieve the recommended dose. A 5-minute rest between the use of devices is recommended.

» Esketamine (an active isomer of ketamine, an N-methyl-D-aspartate [NMDA] receptor antagonist) may be considered by a consultant for depression with acute suicidal ideation or behaviour, as an adjunct to an oral antidepressant.

» Although esketamine is being used more frequently in clinical practice, questions remain about which patients respond best to it, how long therapeutical effects might persist, and over what duration to continue treatment. While no longer considered a last resort treatment, esketamine is not a first- or second-line treatment.

» Availability of esketamine varies according to country of practice and relevant regulatory approval. In the US, the drug is only available through a restricted distribution programme.

» 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, respiratory depression, difficulty with attention, judgement and thinking (dissociation), suicidal thoughts and behaviours, and the potential for drug misuse. Monitor respiratory status and blood pressure during treatment.

» 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. Esketamine is contraindicated in patients with aneurysmal vascular disease, arteriovenous malformation, or intracerebral haemorrhage.

» Use of esketamine nasal spray beyond 4 weeks is not currently supported by evidence,

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given that its effectiveness beyond 4 weeks has not yet been evaluated.

adjunct **electroconvulsive therapy (ECT)**

Treatment recommended for SOME patients in selected patient group

» ECT may be an option for those who have not responded to, or cannot tolerate, antidepressants.[165] The response rate is better for patients with severe major depression than for moderate or mild depression.[177] The potential impact on memory and cognition, which may reduce functioning during active treatment, make ECT less desirable for patients with milder depression. ECT is often the treatment of choice for severely depressed people with late-life depression, because it is effective, and avoids complications that may arise from pharmacological intolerance and drug interactions associated with treatment for comorbid physical conditions.[178]

» ECT is performed under general anesthesia, typically 2 or 3 times a week for a total of 6-12 treatments.[188]

» Patient and clinician must be fully informed of the potential risks, including the risks associated with not having ECT, so that the patient can provide informed consent.[165] The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments, meaning that it is one of the safer procedures performed under general anesthetic.[189] [190] Overall, there is no increase in risk of medical complications in patients receiving ECT versus equally depressed patients not receiving ECT.[191] ECT affects heart rate and blood pressure. Chest pain, arrhythmias, persistent hypertension, and ECG changes have been reported as complications, particularly in patients with pre-existing cardiac disease.[192] Cardiovascular conditions should be stabilised before administering ECT.[192] The majority of patients report adverse cognitive effects during and shortly after treatment, most commonly memory loss (both anterograde and retrograde amnesia).[194] This impairment seems to be short-lived according to objective assessment, although a significant proportion of patients report persistent memory loss following ECT.[193] [194] This potential risk must be balanced against the evidence in favour of its efficacy, especially in patients with severe depression. If a person with depression cannot give informed consent for ECT, it should only be given when it does not conflict with a

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valid advance treatment decision made by the person.[165]

» ECT treatment effects are temporary; following successful treatment, the effect must be maintained by the use of antidepressants and/or maintenance electroconvulsive treatments (typically once per week to once every 4 weeks or longer, titrated to stability).[195] Combined with antidepressants, lithium has been shown to reduce the risk for relapse post-ECT.[319]

less severe depression (PHQ <16): non-pregnant

1st **active monitoring**

» 'Less severe depression' has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of less than 16.[165] This category includes both subthreshold and mild symptoms.

» Treatment decisions are informed by a number of important real-world considerations, including access to psychological treatment, which may be limited or non-existent in some locations. Furthermore, people with depression may have a strong preference for psychological therapy or pharmacotherapy. Research to guide evidence-based individualised treatment is at an early stage.[179] Choice of treatment is therefore highly individualised and empirically validated.

» For people with subthreshold and mild symptoms, the prognosis is often good without the need for pharmacotherapy or formal psychological therapy.[176] [229] For people with less severe depression who do not want treatment, or who feel that their depressive symptoms are improving, an initial period of active monitoring may be appropriate, with review after 2-4 weeks, with advice given to seek medical input if symptoms worsen, and the option to consider treatment at any time if needed.[165] This approach may facilitate further assessment, monitoring and shared decision-making.

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» Psychoeducation alone can achieve remission for some people with less severe depression.[230]

» For all people with depression, psychoeducation and lifestyle advice is

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recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

1st **supportive interventions**

» 'Less severe depression' has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of less than 16.[165] This category includes both subthreshold and mild symptoms.

» Treatment decisions are informed by a number of important real-world considerations, including access to psychological treatment, which may be limited or non-existent in some locations. Furthermore, people with depression may have a strong preference for psychological therapy or pharmacotherapy. Research to guide evidence-based individualised treatment is at an early stage.[179] Choice of treatment is therefore highly individualised and empirically validated.

» For people with less severe depression who wish to consider treatment, guidelines typically recommend non-pharmacological therapies as first-line, based on the assessment that the risk:benefit ratio does not justify the use of pharmacotherapy for mild depression.[165] [197]

» For some patients who have milder symptoms, the degree of impairment or distress from these symptoms might not outweigh the stigma the patients attach to accepting any form of psychiatric treatment; in these patients a focus directly on symptom management may be the optimal strategy.[254] Bibliotherapy, a programme of self-help by reading, may have long-term benefits for some patients.[231]

» Yoga interventions may have a beneficial effect on depressive disorders, but there are

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significant variations in interventions, reporting, and feasibility.[255]

» Other supportive interventions include relaxation training, light therapy, exercise, tai chi, music therapy, and acupuncture.[232] [233] [234] [235] [236][237] [238] [239] [240] [241] [242] In patients with depression, 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.[238] Conversely, cessation of exercise may worsen depressive symptoms.[260] [261]

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

1st **computer-based interventions**

» 'Less severe depression' has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of less than 16.[165] This category includes both subthreshold and mild symptoms.

» Treatment decisions are informed by a number of important real-world considerations, including access to psychological treatment, which may be limited or non-existent in some locations. Furthermore, people with depression may have a strong preference for psychological therapy or pharmacotherapy. Research to guide evidence-based individualised treatment is at an early

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stage.[179] Choice of treatment is therefore highly individualised and empirically validated.

» For people with less severe depression who wish to consider treatment, guidelines typically recommend non-pharmacological therapies as first-line, based on the assessment that the risk:benefit ratio does not justify the use of pharmacotherapy for mild depression.[165] [197]

» Internet- and mobile-based interventions are a promising and rapidly emerging development, and demonstrate efficacy. They may be a useful intervention for people who cannot access or afford or schedule individual or group face-to-face CBT.

» Digital interventions have the potential to widen access to evidence-based care for depression by reaching underserved populations, and may also increase the quality of care by augmenting face-to-face treatment. They may facilitate collaborative care, and shared decision-making.[243] [244] [245] [246] [247] [248] [249] [250]

» The evidence is greatest for internet CBT (iCBT), and suggests that guided iCBT (iCBT supported by human guidance) is as effective as face-to-face CBT.[262] [263]

» Unguided CBT also demonstrates efficacy, but with smaller treatment effect sizes.[244] There may be an increasing role for other types of self-help and self-guided interventions such as behavioural activation strategies, particularly for those with less severe symptoms of depression.[250] [264] [265][266]

» Several key barriers to digital interventions have been noted, including concerns about reduced access to care for people with lower levels of digital literacy; appropriate patient selection is therefore required. There is evidence to suggest that 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.[268]

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails

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educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

1st **psychological therapy**

» 'Less severe depression' has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of less than 16.[165] This category includes both subthreshold and mild symptoms.

» Treatment decisions are informed by a number of important real-world considerations, including access to psychological treatment, which may be limited or non-existent in some locations. Furthermore, people with depression may have a strong preference for psychological therapy or pharmacotherapy. Research to guide evidence-based individualised treatment is at an early stage.[179] Choice of treatment is therefore highly individualised and empirically validated.

» For people with less severe depression who wish to consider treatment, guidelines typically recommend non-pharmacological therapies as first-line, based on the assessment that the risk:benefit ratio does not justify the use of pharmacotherapy for mild depression.[165] [197]

» Psychological therapy appears to have a positive impact on the quality of life of patients with depression, beyond measurable reductions in depressive symptom severity.[269] Mild depression treated with psychotherapy may be less likely to progress to severe depression.[271]

» Psychological treatments may be delivered via different methods and settings, and may include individual, group, or virtual sessions. No clear differences in efficacy have been found among different types of psychological therapies used for depression.[217] Less intensive psychological therapies such as guided self-help

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and group CBT or behavioural activation may be reasonable initial options in this group.[165]

» Note that US-based guidance from the American College of Physicians only recommends CBT, citing insufficient evidence to support other types of psychological therapies.[197]

» Cognitive behavioural therapy (CBT) has shown greater efficacy than pharmacological placebo across levels of severity.[219] Treatment response to CBT is comparable with antidepressant response in some studies.[170] [Evidence B] 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.[335] [336] [337] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[338] CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[175] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[220]

» Other types of psychological therapy for less severe depression include interpersonal psychotherapy (IPT), problem-solving therapy (PST), behavioural activation, and mindfulness-based therapy.[165]

» IPT requires the patient to have psychological insight.[221] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. IPT may improve interpersonal functioning, and also appears effective for relapse prevention.[222] PST focuses on training in adaptive problem-solving attitudes and skills.[223] [224] [225] Results from PST are comparable to those from CBT in primary care settings.[226]

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible.

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This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

1st **antidepressant**

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

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» 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

OR

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

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OR

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

» 'Less severe depression' has been defined by NICE in the UK as a Patient Health Questionnaire (PHQ) score of less than 16.[165] This category includes both subthreshold and mild symptoms.

» For people with less severe depression who wish to consider treatment, guidelines typically recommend non-pharmacological therapies as first-line, based on the assessment that the risk:benefit ratio does not justify the use of pharmacotherapy for mild depression.[165] [197] However note that, as for all patients with depression, there may be reasons to consider pharmacological treatment from the offset in this group in certain specific circumstances (e.g., when there is a history of severe depression, where there is a lack of access to psychological treatment, when the patient has a preference for pharmacotherapy, or when there is a history of a previous positive treatment response to pharmacotherapy). An antidepressant may be preferable in some patients as it may offer a more rapid response than a non-pharmacological treatment.

» Treatment decisions are informed by a number of important real-world considerations, including access to psychological treatment, which may be limited or non-existent in some locations. Furthermore, people with depression may have a strong preference for psychological therapy or pharmacotherapy. Research to guide evidence-based individualised treatment is at an early stage.[179] Choice of treatment is therefore highly individualised and empirically validated.

» US guidance recommends that initial pharmacological treatment should be with a second-generation antidepressant. This may include a selective serotonin-reuptake inhibitor (SSRI; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline); a serotonin-noradrenaline reuptake inhibitor (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).[197] UK

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guidance recommends offering an SSRI as first-line treatment for most people with depression for whom pharmacological treatment is suitable.[165] SNRIs are recommended by NICE as a later-line option.[165] According to UK guidance, clinicians should only consider prescribing vortioxetine when there has been no or limited response to at least 2 previous antidepressants.[165]

» The most commonly prescribed antidepressants, SSRIs and SNRIs, offer similar response rates and can be used first line as monotherapy in mild to moderate depression.[378] No consistent differences in safety or efficacy have been demonstrated between antidepressants.[202] [203] While a few meta-analyses of comparative treatment efficacy have favoured one drug over others, by and large they are comparable in efficacy.[204] [205]

» Choice of drug should be based on patient preference, tolerability, safety in overdose, presence of other psychiatric illness, and past evidence of effectiveness in the patient.[181]

» Depressed patients with undiagnosed bipolar affective disorder may convert to frank mania if they receive antidepressants. 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.

» There is some evidence of increased suicidal thoughts and behaviour in the first weeks of treatment, particularly in teenagers and young adults, and in those on relatively high starting doses.[210] [211] [212] [213] This association is not necessarily causal and may instead be attributable to confounding factors.[214] Close monitoring and risk management is recommended when prescribing an antidepressant to a person under the age of 25 years, or to anybody thought to be at increased risk for suicide.[165]

» 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. Titrate the antidepressant dose to the maximum tolerated in patients who experience a partial response after 2-4 weeks. Patients may begin to show a response within the first 1-2 weeks of

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treatment; however, one fifth of those who have not previously responded may begin to respond after week 5.[216] Successful antidepressant therapy to the point of remission of all symptoms may be expected to 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 6-12 months following remission, before considering discontinuation.[165] [322] However, some treatment guidelines recommend that patients with frequent recurrences and relapses, who respond successfully to antidepressant treatment, may require longer-term or indefinite pharmacological therapy, following shared decision-making.[332]

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

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

2nd **increase antidepressant dose or switch to alternative treatment**

» If the response to first-line therapy is inadequate, initial steps include reassessing the diagnosis, evaluating comorbidities, and exploring adherence to treatment.[277]

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» For those already being treated with an antidepressant, continue treatment if there has been some improvement for at least the full 6-8 weeks. If the response is still incomplete, and if the drug is well-tolerated, and not already above the threshold of safe dose, consider increasing the dose. 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.[278]

» Another option to consider for those already receiving pharmacotherapy is switching to an alternative antidepressant.[279] [280] Switching may be appropriate if no improvement in symptoms has occurred within the first 2 weeks of treatment.[281] [282] However, early response may be, but is not necessarily, a reliable indicator of continued response.[283] [284]

» Switching between antidepressants within a class may be considered initially (e.g., from one selective serotonin-reuptake inhibitor [SSRI] to another SSRI).[181] Next consider a change in drug class; for example, if a patient was on an SSRI, then consider a serotonin-noradrenaline reuptake inhibitor [SNRI].[181] If treatment was not tolerated due to adverse effects, retry with an agent with fewer or different adverse effects. If an agent is switched, resume weekly follow-up until a response is apparent.

» Caution is required when switching from one antidepressant to another due to the risk of drug interactions, serotonin syndrome, withdrawal symptoms, or relapse. See Serotonin syndrome .

» 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

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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.

» Switching from pharmacotherapy to a psychological therapy, or from a pharmacological therapy to pharmacotherapy, may be another reasonable option to consider, as guided by patient preference and access to CBT.[197]

» Continue successful antidepressant treatment for 6-12 months following remission, before continuing discontinuation.[165] [322] However, some treatment guidelines recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require longer-term or indefinite pharmacological therapy, following shared decision-making.[332]

» 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.

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking,

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excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

treatment-resistant/refractory depression

1st

reassess and switch to alternative antidepressant or combination therapy

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

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» 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

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OR

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

OR

» desipramine: 50-75 mg orally once daily at bedtime initially, increase gradually according to response, maximum 200-300 mg/day (may give in divided doses)

OR

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

OR

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

OR

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

Secondary options

» esketamine nasal: (28 mg/device) induction phase: 56-84 mg intranasally twice weekly for 4 weeks, adjust dose based on response and tolerability; maintenance phase: 56-84 mg intranasally once weekly for 4 weeks, followed by 56-84 mg every 1-2 weeks
Dose frequency should be individualised to the least frequent dose to maintain remission/response. Evaluate benefit after 4 weeks before continuing treatment. Each device contains 2 sprays (1 spray for each nostril) and delivers a total of 28 mg per device. Use of 2 or 3 devices is required to achieve the recommended dose. A 5-minute rest between the use of devices is recommended.

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OR

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

OR

» phenelzine: 15 mg orally three times daily initially, increase gradually according to response, maximum 60-90 mg/day; reduce dose gradually over several weeks to lowest effective dose after clinical response

OR

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

OR

» tranylcypromine: 10 mg orally three times daily initially for 2 weeks, increase gradually according to response, maximum 60 mg/day

» Evidence to guide treatment decisions when people with depression do not respond to initial treatments is very limited.[285] [286] The majority of patients with depression do not reach full remission after their first antidepressant trial, but a substantial proportion of those will respond to a second or third antidepressant.[280] The terms 'treatment-refractory' or 'treatment-resistant' depression have been used variously, and somewhat inconsistently, to denote depressive illness that has not remitted after two antidepressant trials of adequate dose and duration.[287] [288] An alternative term has been proposed to emphasise less the binary response of remission or non-remission and more the common scenario of partial, or inconsistent, treatment response: 'difficult-to-treat depression'.[289]

» Guidelines typically recommend that primary care physicians seek specialist input after two unsuccessful treatment interventions, where feasible.[182] [290] Comorbid medical conditions, and psychosocial factors such as temperamental vulnerabilities, behaviour patterns, and life circumstances, may all make depression more difficult to treat.

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» Reassessment can be useful after an apparently failed course of treatment, because some of the residual symptoms of depression (e.g., social avoidance, sleep/wake reversal, feelings of hopelessness) can reflect behavioural adaptations to depression, rather than the depression itself. In such cases, symptoms may best be ameliorated through behavioural intervention or psychological therapy rather than a new medication trial. Cognitive deficits after remission of symptoms are common.[292] These may warrant monitoring and, if appropriate, the patient may benefit from reassurance that there may be continued improvement over time.

» With intermittent, brief follow-up visits it is also easy to miss mood-cycling that may occur between sessions that would indicate a bipolar spectrum disorder rather than pure major depression. Consider diagnostic re-evaluation or whether there may have been issues around adherence with treatment, or if factors such as substance use, 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). The process of switching antidepressants, if undertaken, provides a window of opportunity for combined antidepressant therapy (i.e., an SSRI or SNRI plus bupropion or mirtazapine) while crossing over from one to the other. However, there are little data to support the efficacy of antidepressant combinations.[294] [295] [296] [297] One notable exception to these observations is an apparently synergistic effect when the second antidepressant adds presynaptic alpha-2 receptor antagonism (e.g., mirtazapine, trazodone); however, as in other combination strategies, patient retention in treatment drops when additional drugs are added.[298]

» A specialist may prescribe two (or in rare cases more) antidepressants 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

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functioning). There is some evidence that failure on one or several antidepressants does not preclude later success.[279] [280] 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.[282]

» 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. UK guidance states that TCAs should only be prescribed for depression by a specialist clinician (e.g., psychiatrist) working in secondary care.[165]

» Esketamine (an active isomer of ketamine, an N-methyl-D-aspartate [NMDA] receptor antagonist) may be considered by a consultant as monotherapy for treatment-resistant depression. Evidence has demonstrated the rapid efficacy of esketamine monotherapy; within one randomised controlled trial (RCT), within the first 24 hours of the initial dose, participants experienced significant improvements in their Montgomery-Asberg Depression Rating Scale (MADRS) total score, with the effects persisting for at least 4 weeks. By the fourth week, 22.5% of patients receiving esketamine had achieved remission (MADRS total score ≤12), compared to 7.6% in the placebo group.[379] Although esketamine is being used more frequently in clinical practice, a cautious approach is advised, questions remain about which patients respond best to it, how long therapeutical effects might persist, and over what duration to continue treatment. While no longer considered a last resort treatment, esketamine is not a first- or second-line treatment. Availability of esketamine varies according to country of practice and relevant regulatory approval. In the US, the drug is only available through a restricted distribution programme. The drug must be self-administered by the patient, who is supervised

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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, respiratory depression, difficulty with attention, judgement and thinking (dissociation), suicidal thoughts and behaviours, and the potential for drug misuse. Monitor respiratory status and blood pressure during treatment. 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. Esketamine is contraindicated in patients with aneurysmal vascular disease, arteriovenous malformation, or intracerebral haemorrhage.

» In cases where nothing else has worked and the patient can tolerate a washout period from their current antidepressant, monotherapy with 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.[299] [300] The washout period depends on the half-life of the antidepressant the patient is currently on and can range from 1 to 5 weeks. 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. The combination of a MAOI with another antidepressant is not recommended, and certain combinations are contraindicated, owing to severe risks (e.g., serotonin syndrome). They are generally not used in primary care; do not use an MAOI without consulting a psychiatrist first.[165]

» 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 pharmacokinetical 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

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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 6-12 months following remission, before considering discontinuation.[165] [322] A possible exception is the use of esketamine nasal spray, as current evidence on longer-term use is limited and its effectiveness beyond 4 weeks has not yet been evaluated.

» Some physicians recommend that patients with frequent previous recurrences and relapses, who respond successfully to antidepressant treatment, may require longer-term or indefinite therapy, following shared decision-making.[332]

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

plus **consider augmentation pharmacotherapy**

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

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OR

» brexpiprazole: consult specialist for guidance on dose

OR

» cariprazine: consult specialist for guidance on dose

» In patients who have not responded to conventional antidepressants, lithium augmentation is an evidence-based approach.[302] Lithium augmentation is initiated by a psychiatrist because of its narrow therapeutic index and risks of inadvertent toxicity from excessive dosing and drug-drug interactions. Augmentation with some antipsychotic agents may improve outcomes.[304] [305] [380] However, one cohort study reported increased mortality risk in general associated with adding an antipsychotic versus adding a second antidepressant.[308] It is unclear whether this is a pharmacological effect of antipsychotics or a reflection of the likelihood that antipsychotics tend to be prescribed to patients who are at higher risk for mortality for other reasons. Because of this potential risk, augmentation with an antipsychotic for treatment-resistant depression should typically be overseen by a psychiatrist who can determine the clinical necessity of choosing it over other strategies.

» Evidence better supports short-term versus long-term use of adjunctive antipsychotics.[309] Long-term use exposes patients to common antipsychotic side effects such as weight gain, akathisia, and, rarely, tardive dyskinesia. This concern applies as well to new agents such as brexpiprazole, which are similar to antipsychotics structurally but are marked specifically for use in treatment-resistant depression. Although deemed effective (in a small number of studies), the side effects are similar to other antipsychotics, and so it is important to consider whether benefits outweigh risks in people without psychosis.[310] [311] [312] [313] [314]

» If the patient is not already on esketamine nasal spray monotherapy first line, it may be considered by a consultant as an augmentation strategy (to be used with an oral antidepressant) for treatment-resistant depression.

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» Other augmentation strategies may be used by specialists.[316] [317] [318]

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

plus **psychological therapy or other non-pharmacological treatment**

Treatment recommended for ALL patients in selected patient group

» Check and ensure that the patient has started psychological therapy if multiple pharmacological agents have been unsuccessful; in particular, cognitive behavioural therapy (CBT) appears to be effective at reducing symptoms in treatment-resistant depression with long-lasting results (up to at least 1 year).[293]

» Psychological therapy has been shown to be both effective and cost-effective in reducing depressive symptoms.[167] [168] Psychological therapy is as efficacious as pharmacotherapy and reduces the risk of relapse when added to pharmacotherapy.[169] [377] Psychological interventions may reduce the number of sickness absence days from work, whether this is face to face or online.[163]

» CBT has shown greater efficacy than pharmacological placebo across levels of severity.[219] Treatment response to CBT is comparable with antidepressant response in some studies.[170] [Evidence B] 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.[335] [336] [337] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[338] CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[175] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[220]

» Other types of psychological therapy for depression include interpersonal psychotherapy (IPT), problem-solving therapy (PST), behavioural activation, and bibliotherapy. IPT requires the patient to have psychological insight.[221] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. IPT

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may improve interpersonal functioning, and also appears effective for relapse prevention.[222] PST focuses on training in adaptive problem-solving attitudes and skills.[223] [224] [225] Results from PST are comparable to those from CBT in primary care settings.[226]

» 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. A Cochrane review found it to be equally effective to CBT for adults with depression, albeit with a low level of certainty given the evidence available.[227]

» Bibliotherapy, a programme of self-help by reading, may have long-term benefits for some patients.[231]

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

2nd **electroconvulsive therapy (ECT)**

» ECT may be an option for those who have not responded to, or cannot tolerate, antidepressants.[165] Although listed here as a secondary option, note that treatment decisions are highly individualised, and ECT may be considered early in the course of treatment in some people with severe depression. Indications for early use include treatment for depression with psychotic symptoms, suicidality, or catatonia, or where there has been a previous positive treatment response to ECT.[165] [177]

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» The response rate is better for patients with severe major depression than for moderate or mild depression.[177] The potential impact on memory and cognition, which may reduce functioning during active treatment, make ECT less desirable for patients with milder depression. ECT is often the treatment of choice for severely depressed people with late-life depression, because it is effective, and avoids complications that may arise from pharmacological intolerance and drug interactions associated with treatment for comorbid physical conditions.[178]

» ECT is performed under general anesthesia, typically 2 or 3 times a week for a total of 6-12 treatments.[188]

» Patient and clinician must be fully informed of the potential risks, including the risks associated with not having ECT, so that the patient can provide informed consent.[165] The mortality rate of ECT is estimated to be about 2 deaths per 100,000 treatments, meaning that it is one of the safer procedures performed under general anesthetic.[189] [190] Overall, there is no increase in risk of medical complications in patients receiving ECT versus equally depressed patients not receiving ECT.[191] ECT affects heart rate and blood pressure. Chest pain, arrhythmias, persistent hypertension, and ECG changes have been reported as complications, particularly in patients with pre-existing cardiac disease.[192] Cardiovascular conditions should be stabilised before administering ECT.[192] The majority of patients report adverse cognitive effects during and shortly after treatment, most commonly memory loss (both anterograde and retrograde amnesia).[194] This impairment seems to be short-lived according to objective assessment, although a significant proportion of patients report persistent memory loss following ECT.[193] [194] This potential risk must be balanced against the evidence in favour of its efficacy, especially in patients with severe depression. If a person with depression cannot give informed consent for ECT, it should only be given when it does not conflict with a valid advance treatment decision made by the person.[165]

» ECT treatment effects are temporary; following successful treatment, the effect must be maintained by the use of antidepressants and/or maintenance electroconvulsive treatments (typically once per week to once every 4 weeks or longer, titrated to stability).[195] Combined

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with antidepressants, lithium has been shown to reduce the risk for relapse post-ECT.[319]

plus **psychological therapy or other non-pharmacological treatment**

Treatment recommended for ALL patients in selected patient group

» Check and ensure that the patient has started psychological therapy if multiple pharmacological agents have been unsuccessful; in particular, cognitive behavioural therapy (CBT) appears to be effective at reducing symptoms in treatment-resistant depression with long-lasting results (up to at least 1 year).[293]

» Psychological therapy has been shown to be both effective and cost-effective in reducing depressive symptoms.[167] [168] Psychological therapy is as efficacious as pharmacotherapy and reduces the risk of relapse when added to pharmacotherapy.[169] [377] Psychological interventions may reduce the number of sickness absence days from work, whether this is face to face or online.[163]

» CBT has shown greater efficacy than pharmacological placebo across levels of severity.[219] Treatment response to CBT is comparable with antidepressant response in some studies.[170] [Evidence B] 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.[335] [336] [337] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[338] CBT appears to have an enduring effect that reduces subsequent risk after treatment ends.[175] Adjunctive CBT has also been found to improve outcomes for depression treatment in the primary care setting.[220]

» Other types of psychological treatment for depression include interpersonal psychotherapy (IPT), problem-solving therapy (PST), behavioural activation, and bibliotherapy. IPT requires the patient to have the capacity for psychological insight.[221] Frequency for both CBT and IPT is determined by the healthcare provider. The time to response is approximately 12 weeks. IPT may improve interpersonal functioning, and also appears effective for relapse prevention.[222] PST focuses on training in adaptive problem-solving attitudes and skills.[223] [224] Results from PST are

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comparable to those from CBT in primary care settings.[226]

» 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. A Cochrane review found it to be equally effective to CBT for adults with depression, albeit with a low level of certainty given the evidence available.[227]

» Bibliotherapy, a programme of self-help by reading, may have long-term benefits for some patients.[231]

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be re-inforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

pregnant

1st **active monitoring and/or antidepressant and/or electroconvulsive therapy (ECT)**

» Less severe depression: when the maternal and fetal risk of untreated depression is low, the risk/benefit balance may tip in favour of non-pharmacological therapies, as reflected in several treatment guidelines worldwide.[358] [362]

» More severe depression: studies of the safety of antidepressant use in pregnancy for the most part add up to minimal risk to the fetus.[340] [341] There is little controlled trial evidence. Consistent data to support fully

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informed decision-making are lacking. Cohort studies have reported a small increased risk of pre-eclampsia, postnatal haemorrhage, and gestational diabetes in women who continue antidepressants throughout pregnancy.[342] [343] Based on mixed evidence for an increased risk of postnatal haemorrhage associated with antidepressants, the UK government has advised caution.[344]

» Women who stop their antidepressant are more likely to have a relapse of depression during their pregnancy.[345] [346] UK national enquiry data show that in women in contact with UK psychiatric services, peinatal suicides are more likely to occur in those with a depression diagnosis and no active treatment at the time of death.[347]

» 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.[348]

» For infants exposed to antidepressants during pregnancy, evidence as to whether there is an increased risk of preterm birth and low birth weight compared to infants of mothers with untreated depression is mixed.[343] [349] [350] [351][352] There is a small increased risk of persistent pulmonary hypertension of the newborn with maternal SSRI and SNRI use in any trimester (number needed to harm = 100).[356] [357]

» Clinicians and patients should 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. In the US, such discussions are frequently carried out by the patient's obstetrician; obstetricians in the US may seek further specialist treatment advice from Perinatal Psychiatry Access Programs where available.[358] In other locations (e.g., the UK) clinicians should consult a specialist with experience in perinatal mental health as part of this process. The American College of Obstetricians and Gynecologists (ACOG) recommends that if pharmacological treatment is required for perinatal depression, selective serotonin-reuptake inhibitors (SSRIs) may be used as first-line pharmacotherapy, and serotonin-noradrenaline reuptake inhibitors (SNRIs) are reasonable alternatives.[358]

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» Some classes of antidepressants, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), are not routinely used for depression in pregnancy, owing to concerns about potential risks to the mother and baby.[358] Esketamine nasal spray is a relatively new drug and is not recommended in pregnancy, as studies involving pregnant animals treated with ketamine indicate that esketamine may cause harm to the fetus when used during pregnancy.

» 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] (http://www.uktis.org)

» Severity of depressive symptoms may influence treatment choice. In very severe depression in pregnancy, electroconvulsive therapy (ECT) may the treatment of choice when the severity of illness puts the fetus at risk either due to poor maternal self-care or suicide. There is no known risk to the fetus from ECT.[359] [360]

plus **psychological therapy**

Treatment recommended for ALL patients in selected patient group

» Psychological treatments have essentially no risk of side effects and may be offered as monotherapy as one first-line option for depression occurring in pregnancy, particularly for those with less severe depression, or as adjunctive therapy for people receiving other treatments.[358]

» 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.[364]

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the

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nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

Ongoing

treatment responsive

1st **maintenance antidepressant and/or psychological therapy**

» For patients established on antidepressants, regularly review their antidepressant use to assess efficacy and the presence of any adverse effects, and to ensure that long-term use remains clinically indicated.[272]

» Shared decision-making is recommended; options for those already taking an antidepressant who have achieved full or partial remission are; continuing antidepressant treatment; switching to a psychological treatment for relapse prevention; or continuing with the same antidepressant and adding on a psychological treatment for relapse prevention.[165]

» Maintenance on antidepressants following remission does not guarantee protection from relapse, but there is evidence of at least a modest benefit.[331] Continue the antidepressant regimen that led to remission for 6-12 months following remission.[165] [322] The World Federation of Societies of Biological Psychiatry (WFSBP) supports the use of maintenance treatment for recurrent depression in some circumstances; WFSBP recommends maintenance treatment for 5-10 years, or indefinitely, for those people at greater risk of recurrent depression, particularly when two or three attempts to withdraw pharmacotherapy have been followed by another episode within a year.[322]

» There is a growing body of evidence to support the use of psychological therapy for prevention of relapse and recurrence, both used alone and in combination with pharmacotherapy.[175] [333] Specific modalities with demonstrated efficacy for relapse prevention include preventive CBT, mindfulness-based CBT, and interpersonal therapy (IPT).[165] [334] 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.[335] [336] [337] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[338]

» Continued psychotherapy with antidepressant management is an effective option when

Ongoing

continued through both acute and ongoing phases of treatment.[173]

» There is evidence that switching in the maintenance phase from pharmacotherapy to psychotherapy can be at least as effective in preventing relapse as staying with pharmacotherapy.[182] [333] [339]

» Computerised CBT is recommended by some international guidelines for relapse prevention in patients with mild depression.[182]

» If discontinuation of a selective serotonin-reuptake inhibitor (SSRI) or a serotonin-noradrenaline reuptake inhibitor (SNRI) is required, the most immediate concern when removing a patient from antidepressant therapy is the possibility of rapid relapse. Beyond that, some antidepressants, particularly those in the SSRI or SNRI classes, are associated with a 'discontinuation syndrome'. Typical are flu-like symptoms, hyperarousal, insomnia, vertigo, and sensory disturbances (e.g., 'brain zaps'). Patients will often know how vulnerable they are to these symptoms, if they have ever skipped a dose or run out of their medication.

» Slowly decrease the dose to reduce the risk of unpleasant discontinuation symptoms; this can usually be done over several weeks, but in some cases may take several months or longer in particularly susceptible patients.[324] [328]

» Drugs with shorter half-lives (e.g., paroxetine, venlafaxine) may require longer periods of taper.[329] A proportionate method of tapering is recommended by some treatment guidelines; this involves reductions as a proportion of the previous dose (e.g. 25%) rather than reducing the dose by a fixed increment each time.[165] If the required dose is not available in tablet form, a liquid preparation may be required (if available).

» Be aware that people's experiences of withdrawal symptoms can vary substantially from mild and transient to longer-lasting and more severe. Anticipatory discussion with the patient is important, including when and how to seek support from a healthcare professional in the event of discontinuation symptoms.[329] Closely monitor the patient to ensure that any apparent emerging discontinuation symptoms do not in fact represent a relapse of their depression.[272] [330]

plus **psychoeducation and lifestyle advice**

Ongoing

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

recurrent episode

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

» Recurrent episodes of major depression should be treated with the same regimen that previously led to remission, provided that the recurrence did not occur while under adequate maintenance treatment with such medication.

» The World Federation of Societies of Biological Psychiatry (WFSBP) supports the use of pharmacological maintenance treatment for recurrent depression in some circumstances; WFSBP recommends maintenance treatment for 5-10 years, or indefinitely, for those people at greater risk of recurrent depression, particularly when two or three attempts to withdraw pharmacotherapy have been followed by another episode within a year.[332] The selection and success of these treatments depends on the type and severity of depressive symptoms, but most often relies on trial and error.

» There is a growing body of evidence to support the use of psychological therapy for prevention of relapse and recurrence, both used alone and in combination with pharmacotherapy.[175] [333] Specific modalities with demonstrated efficacy for relapse prevention include preventive CBT, mindfulness-based CBT, and interpersonal therapy (IPT).[165] [334] Staged treatment trials suggest that CBT may be particularly beneficial when used during the continuation phase of

Ongoing

treatment; CBT reduces the risk of relapse/recurrence at least as well as, and perhaps better than, antidepressant continuation.[335] [336] [337] In pooled clinical trials, mindfulness-based CBT was found to be particularly useful in relapse prevention.[338]

» Continued psychotherapy with antidepressant management is an effective option when continued through both acute and ongoing phases of treatment.[173]

» There is evidence that switching in the maintenance phase from pharmacotherapy to psychotherapy can be at least as effective in preventing relapse as staying with pharmacotherapy.[182] [333] [339]

» Computerised CBT is recommended by some international guidelines for relapse prevention in patients with mild depression.[182]

plus **psychoeducation and lifestyle advice**

Treatment recommended for ALL patients in selected patient group

» For all people with depression, psychoeducation and lifestyle advice is recommended at the start of treatment, and may be reinforced during treatment, as required.[165] Psychoeducation entails educating about the nature of the illness and may be beneficial to involve family members whenever feasible. This involvement allows them to gain a better understanding of behaviours like lack of motivation or drive, which might otherwise be misconstrued as 'laziness' or disinterest.[180]

» Lifestyle advice encompasses instruction on the following: sleep hygiene, and setting appropriate times for sleeping and waking; healthy diet and exercise; cessation of smoking, excess intake of alcohol and substance misuse including cannabis use (if cessation is not possible, then advice on moderation is required).[180]

Emerging

Gepirone

Gepirone is an oral, selective serotonin 5-HT1A receptor agonist. Its mechanism of action is not yet fully understood. It has a different mechanism of action to selective serotonin-reuptake inhibitors (SSRIs), which block the reabsorption of serotonin into cells, meaning that it is likely to have a slightly different adverse effect profile to other treatments available for depression, notably with less potential for sexual dysfunction. It is approved by the Food and Drug Administration (FDA) for the treatment of major depressive disorder in adults on the basis of two RCTs which demonstrated superior efficacy compared to placebo, with effect sizes demonstrated similar to those of other approved antidepressants.[381] Gepirone is not yet routinely used in clinical practice. It is currently unclear whether there is a subgroup of patients who may be more likely to respond to gepirone; evidence from a follow-up analysis of clinical trial data suggests that adults with depression with prominent anxiety symptoms (anxious depression) had a greater response than those without prominent anxiety symptoms.[382] Gepirone is not approved in Europe as yet.

New and novel antidepressants

After nearly half a century in which the only standard pharmacological treatments for depression were based on serotonin and noradrenaline neurotransmission, there has been an explosion of promising new methods emerging in the past decade.[383] 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. Dextromethorphan/bupropion has been approved by the US Food and Drug Association (FDA). Dextromethorphan is the first oral N-methyl D-aspartate (NMDA) receptor antagonist (and sigma-1 receptor agonist) to be approved for the treatment of major depressive disorder. It is rapid acting, but the exact mechanism of action in the treatment of depression is unclear. Bupropion is coformulated with dextromethorphan to increase and prolong plasma levels of dextromethorphan via competitive inhibition of cytochrome P450 2D6. Approval followed two positive trial results; the first in which it demonstrated superiority to placebo, and the second in which it demonstrated superiority to bupropion alone. Of note, efficacy of dextromethorphan/bupropion was observed early in the course of treatment (at 1-2 weeks) and sustained following this.[384] [385] Psilocybin, a psychedelic drug, has received breakthrough therapy designation from the FDA for treatment-resistant depression.[386] In one phase 2 trial comparing treatment with psilocybin to treatment with escitalopram, there were similar degrees of improvement in both treatment groups.[387] There is evidence that beneficial effects of psilocybin on depressive symptoms may last at least up to 12 months post-intervention in some patients.[388] A single dose psilocybin regimen has shown evidence of efficacy, according to two RCTs.[389] [390] It has been suggested that the positive benefits are mediated more directly through psychological therapy administered with psilocybin as opposed to a direct pharmacological effect.[391] Nitrous oxide has yielded some preliminary positive results in an open trial.[392] Agomelatine, a melatonin receptor agonist and serotonin 5-HT2c receptor antagonist, has been found to be effective and is available in Europe.[393] The antibiotic minocycline has generated some positive preliminary results when used as an adjunctive treatment with antidepressants, although results are mixed.[394] [395] [396] Targeting minocycline towards people with depression evidence of low-grade systemic inflammation (raised CRP) is an emerging area of research.[397]

Intravenous ketamine

Intravenous ketamine, an NMDA receptor antagonist, along with its inhaled isomer esketamine (see below) have continued to perform better than placebo in alleviating depressive symptoms but are not yet used in standard clinical practice.[398] [399] [400] [401] In case reports, case series, and select trials, ketamine has been shown to have a rapid effect in the reduction of scores on several depression scales.[402] [403] [404] There is some evidence of a sustained antidepressant effect for up to 6 weeks.[405] Intravenous ketamine appears to be more efficacious than intranasal esketamine.[406] However, its safety and efficacy for long-term use remain unknown.[407] [408] Acute side effects are common and are more likely to occur in patients given intravenous ketamine. The majority of side effects resolve shortly after drug administration. They include psychiatric (most commonly anxiety), psychotomimetic, cardiovascular, and neurological effects. The most common somatic effects were headache, dizziness, dissociation, elevated blood pressure, and blurred vision.[409] Repeated use of ketamine in other patient groups has been linked to urological and liver toxicity, cognitive deficits, and dependency.[409]

Transcranial magnetic stimulation (TMS)

Since its introduction in 2008, TMS - the application of a magnetic field across the skull into the brain to induce electrical activity, in daily sessions over the course of 1 to 2 months - has become widely available in some clinical settings. Data support an antidepressant effect of high-frequency repetitive TMS administered to the left pre-frontal cortex, and guidelines for best practice have been developed.[410] [411] [412] Although consensus has emerged about some aspects of the indications and application of the treatment, it remains an emerging treatment because there are many key questions about when, how, and in whom to use it. Compared with antidepressants, TMS entails a high cost in terms of both time and money. For now, it is generally reserved for patients who have not responded to antidepressants. The absence of psychosis and younger age may predict success.[410] Review of literature has found inconsistent evidence of a benefit in depression, and some evidence of a synergistic effect with concurrent antidepressant treatment.[413] [414] [415] [416] [417] [418] 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.[419] Another study suggests that maintenance treatment may enhance the durability of the antidepressant effects of TMS.[420] 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.[421] Work is ongoing to establish whether variation in treatment parameters might affect outcomes.[422] Other evidence suggests that TMS is no different from sham TMS treatment in patients with depression.[423] Large-scale studies are needed.[424]

Stanford neuromodulation therapy (SNT)

SNT is a rapidly acting non-invasive brain stimulation technique, utilising functional MRI-guided targeting, that is given over a 5-day period. It is a variant of a type of TMS utilising intermittent theta-burst stimulation. It is approved by the FDA for adults with treatment resistant major depression, following RCT data demonstrating non-inferiority to the standard, longer TMS protocol, as well as data from an RCT of 29 adults with treatment-resistant depression who experienced an average 62% reduction in Montgomery-Asberg Depression Rating Scale (MADRS) scores following 5 days of treatment, compared to an average 14% drop in MADRS scores in the sham stimulation group.[425] [426]

Vagus nerve stimulation (VNS)

VNS entails stimulation of the left cervical vagus nerve, using a commercial device.[427] 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.[428] The generator is programmed to deliver mild electric pulses in continuous cycles, typically with 30 seconds of stimulation followed by 5 minutes off.[428] 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.[429] [430] Evidence on the efficacy of VNS is mixed.[431] [432] In one long-term follow-up study, however, the benefits of VNS over treatment as usual could still be seen over 5 years.[433]

Deep brain stimulation (DBS)

A neurosurgical intervention, 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.[434] [435] Results are limited by small sample size and insufficient randomised control data.[436] [437] [438]

Transcranial direct current stimulation (tDCS)

A weak electrical current is applied to the scalp, often via a cap. 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, results from other trials have been mixed.[439] [440] 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.[441]

Non-steroidal anti-inflammatory drugs (NSAIDs)

Two systematic reviews and meta-analyses of the efficacy of NSAIDs in depression suggest they may be effective (particularly celecoxib) and safe for this indication, although results are mixed, and further work is needed to determine in which patients NSAIDs might be most effective.[442] [443] [444]

Buprenorphine

Buprenorphine, a partial opioid receptor agonist currently in widespread use in the treatment of opioid addiction, has shown short-term efficacy for treatment-resistant depression.[445] Long-term safety and efficacy data are lacking.

Nutraceuticals

Adjunctive use of pharmaceutical-grade nutrients, such as S-adenosylmethionine (SAMe), acetylcysteine, methylfolate, omega-3 fatty acids, vitamin D, probiotics and others, has been found to be effective in improving antidepressant response in some studies, and adds little if any risk to the patient.[446] [447][448] [449] [450] [451] [452][453] [454] St John's Wort is a herb that may be effective for the treatment of mild to moderate depression.[455] [456] [Evidence C] [Evidence C] However, numerous reports indicate the possibility of clinically significant drug-drug interactions, which must be taken into account if its use is being considered.[457] [458] 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 people with other psychiatric illnesses.[144] 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.[144] [459] [460] One 2×2 factorial randomised clinical trial of multinutrients (omega-3 fatty acids, selenium, folic acid, and vitamin D3 plus calcium), therapy (group or individual), or their combination, given to overweight patients with subsyndromal depressive symptoms showed that multinutrients did not reduce episodes of major depressive disorder over the 1 year.[461]

Pharmacogenetics

The emergence of fast and affordable genetic assays has led to the increasing use of genetic testing to guide selection of antidepressants for depression.[462] 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.[463] 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.[464] [465] However, they have not proven to be cost-effective in practice. Pharmacogenomic analysis is not yet recommended for routine use.[466]

Primary prevention

A World Psychiatric Association Commission on depression prevention has defined three levels of intervention: universal (aimed at a general population), selective (aimed at people who have known depression risk factors), and 'indicated' (targeted to people who already have some depressive symptoms, but not 'major' depressive illness).[28] These may be combined into a staged set of interventions tailored to a given organisation or group.

Psychological and educational interventions (including CBT) have been shown to modestly reduce the risk of progression to depression when targeted at adults at increased risk due to the presence of risk factors, as well as at those with subthreshold symptoms of depression.[113] [114] One meta-analysis looking at CBT-based selective interventions for depression prevention (i.e., targeted towards those at increased risk of depression) found that such interventions were effective; 1 year after the preventive intervention, people had a relative risk of developing depression of 0.81 (95% CI: 0.72 to 0.91), meaning that those who had received the intervention had 19% lower chance of developing a depressive disorder compared to the control group. This corresponds to a number to treat (NNT) of 21, in order to prevent one episode of depression.[115]

Workplace interventions promoting employee control and physical activity, and those utilising CBT-based techniques, also show modest benefits.[116] Workplace interventions which use CBT to target people with subthreshold depressive symptoms have demonstrated small to medium effects.[117] eHealth interventions based on principles of CBT have demonstrated a small positive effect; one meta-analysis demonstrated that universal, selective and indicated eHealth interventions resulted in reduced rates of depression in the general population, although evidence on long-term efficacy is lacking.[118]

Preventative interventions which target lifestyle behaviours such as smoking also show promise for prevention.[119] Exercise has demonstrated antidepressant effects, and so may be a useful intervention to prevent progression to major depressive disorder for those with subthreshold symptoms.[120] [121] [122] [123]

Secondary prevention

Patients and their families must be cautious during the early stages of medicine treatment, as the risk of suicide may temporarily increase. Routinely asking patients about suicidal ideation and reducing access to lethal means (especially firearms) can reduce the risk of suicide.[129] See Suicide risk mitigation .

Pre-emptive antidepressant treatment may prevent depression in medically ill patients, but evidence is uncertain.[484]

Patient discussions

Anyone who is experiencing clinically significant symptoms of depression should be evaluated by a doctor.

Medicines and psychological therapy are the most common treatments. Treatment is very individualised, and depends on a number of factors specific to the person with depression, including treatment availability and their own personal preference.

There are many different types of antidepressants. These medicines may take several weeks before they become effective and should usually be taken for at least 6 months after symptoms go away to prevent symptoms from coming back, and that treatment should be reviewed regularly.[165]

Psychological or talking therapy also helps most patients with depression. Talking therapy helps the patient explore and change the thoughts, attitudes, and relationship problems associated with depression. Some people with depression can be treated effectively with psychological therapy alone. More severe depression often requires both psychological therapy and antidepressants.

Patient education should include warnings about the potential problems associated with the abrupt discontinuation of antidepressants.[330] Advise patients to talk to the healthcare professional who prescribed the antidepressant before stopping treatment.[330]

Advise them that withdrawal symptoms do not affect everyone, and can vary in type and severity between individuals. Symptoms may include:[330]

- Unsteadiness, vertigo or dizziness
- Altered sensations (e.g., electric shock sensations)
- Altered feelings (e.g., irritability, anxiety, low mood tearfulness, panic attacks, irrational fears, confusion, or very rarely suicidal thoughts)
- Restlessness or agitation
- Problems sleeping
- Sweating
- Abdominal symptoms (e.g., nausea)

- Palpitations, tiredness, headaches, and aches in joints and muscles

Monitoring

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.[479] [480] 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.[481] 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, as is text messaging.[482] [483]

Continuation, maintenance, and discontinuation

- 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 maintenance phase, monitor patients monthly in person or by telephone. It is important to continue assessing adherence, suicidality, and adverse effects.
- 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.
- Collaborative care models and digital interventions (e.g., iCBT) may facilitate monitoring. See Management approach .
- Duration of treatment following the remission of symptoms depends on the prior course of illness. Data on treatment outcomes beyond the initial weeks of treatment are limited, although one systematic review suggests that the efficacy of antidepressants compared with placebo is stable over at least the first 6 months of treatment.[320] In general there appears to be a reduced risk of relapse when antidepressants are continued for 6 months or over.[321] [322] [323] Continue successful antidepressant treatment for 6-12 months following remission.[165] [322]
- Discontinuation of antidepressant treatment has consistently been associated with a greater risk of relapse than does continuing treatment, and is therefore a complex clinical decision.[324] [325] [326] For some people at increased risk of relapse, continuation of treatment beyond this period may be required. Shared decision-making is recommended.
- The World Federation of Societies of Biological Psychiatry (WFSBP) supports the use of maintenance treatment for recurrent depression in some circumstances; WFSBP recommends maintenance treatment for 5-10 years, or indefinitely, for those people at greater risk of recurrent depression, particularly when two or three attempts to withdraw medication have been followed by another episode within a year.[332]
- For patients established on pharmacological treatment for depression, regularly review their antidepressant use to assess efficacy and the presence of any adverse effects, and to ensure that long-term use remains clinically indicated.[272]
- If discontinuation of a selective serotonin-reuptake inhibitor (SSRI) or a serotonin-noradrenaline reuptake inhibitor (SNRI) is required, slowly decrease the dose to reduce the risk of unpleasant withdrawal symptoms; this may need to take place over several months or longer, and should be done at a rate that is tolerable to the patient.[324] [328] Drugs with shorter half-lives (e.g., paroxetine, venlafaxine) require longer periods of taper.[329] A proportionate method of tapering is recommended by some treatment guidelines; this involves reductions as a proportion of the previous dose (e.g., 25%) rather than reducing the dose by a fixed increment each time.[165] If the required dose is not available in tablet form, a liquid preparation may be required (if available). Be aware that people's experiences of withdrawal symptoms can vary substantially from mild and

transient to longer-lasting and more severe. Anticipatory discussion with the patient is important, including when and how to seek support from a healthcare professional in the event of withdrawal symptoms.[329] Closely monitor the patient to ensure that any apparent emerging withdrawal symptoms do not in fact represent a relapse of their depression.[272] [330]

- There is a growing body of evidence supporting the use of psychological therapy for prevention of relapse and recurrence, both when used alone and in combination with pharmacotherapy.[175] [333] Specific modalities with demonstrated efficacy for relapse prevention include preventive CBT, mindfulness-based CBT, and interpersonal therapy (IPT).[334] There is evidence that switching in the maintenance phase from pharmacotherapy to psychotherapy can be at least as effective in preventing relapse as staying with pharmacotherapy.[333] [339]

Complications

Complications	Timeframe	Likelihood
sexual adverse effects of selective serotonin-reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs)	**short term**	**medium**
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.[470] [471] Note that there is growing recognition of a more persistent negative impact on libido of these medications in some patients persisting after drug discontinuation; however, it remains poorly understood and characterised.[472]		
risk of self-injurious behaviour	**short term**	**medium**
Children, adolescents, and young adults may experience a transient increase in risk for self-injury, most severe with rapid escalation in dosing.[210] Close monitoring and risk management is recommended when prescribing an antidepressant to a person under the age of 25 years, or to anybody thought to be at increased risk for suicide.[165]		
undesired weight gain from antidepressants	**short term**	**low**
Weight gain is most common with mirtazapine but can also be seen with SSRIs, venlafaxine, and tricyclic antidepressants. Patient may be switched to bupropion.		
agitation or excessive activation from antidepressants	**short term**	**low**
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.		
unmasking mania	**short term**	**low**
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.[473] Depressed patients with undiagnosed bipolar affective disorder may convert to frank mania if they receive antidepressants. 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.[474]		
mania due to antidepressant withdrawal	**short term**	**low**
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.[475] 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.[476]		

FOLLOW UP

Complications	Timeframe	Likelihood
antidepressant discontinuation syndrome	**short term**	**low**
It occurs after discontinuation of an antidepressant that was taken for at least 6 weeks. Typical symptoms include influenza-like symptoms, hyperarousal, insomnia, vertigo, and sensory disturbances (e.g., 'brain zaps'). Patients will often know how vulnerable they are to these symptoms, if they have ever skipped a dose or run out of their medication. Clinicians should slowly decrease the dose to reduce the risk of unpleasant discontinuation symptoms; this can usually be done over several weeks, but in some cases may take several months or longer in particularly susceptible patients.[324] [328]		
risk of suicide with SSRI treatment	**variable**	**low**
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.[213] [477] [478] Close monitoring and risk management is recommended when prescribing an antidepressant to a person under the age of 25 years, or to anybody thought to be at increased risk for suicide.[165]		

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.[165] [322] Depression lasting more than 12 months occurs in approximately 12% of patients according to community studies, and in up to 61% of patients treated in secondary care.[467]

Depression may be intermittent and recurrent across the lifespan.[468] For patients who are established on antidepressants clinical guidance supports consideration of prolonged antidepressant treatment and psychological therapy for relapse prevention, either alone or in combination.[165] [332]

Depression recurs in about one third of patients within 1 year of discontinuing treatment and in more than 50% of patients during their lifetime.[39] Evidence that antidepressants can prevent relapse is unclear.[469] After 15 years, 87% will experience a recurrence. For patients with multiple recurrent depressive episodes, many experts advocate long-term maintenance therapy.[332]

Diagnostic guidelines

United Kingdom

Perinatal mental health conditions (https://www.sign.ac.uk/our-guidelines/perinatal-mental-health-conditions)

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2023

Depression in adults: treatment and management (https://www.nice.org.uk/guidance/ng222)

Published by: National Institute for Health and Care Excellence **Last published:** 2022

International

WHO Clinical descriptions and diagnostic requirements for ICD-11 mental, behavioral and neurodevelopmental disorders (CDDR) (https://www.who.int/publications/i/item/9789240077263)

Published by: World Health Organization (WHO) **Last published:** 2024

North America

Screening and diagnosis of mental health conditions during pregnancy and postpartum (https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2023

Depression and suicide risk in adults: screening (https://www.uspreventiveservicestaskforce.org/uspstf)

Published by: US Preventive Services Task Force **Last published:** 2023

Screening and intervention for mental health disorders and substance use and misuse in the acute trauma patient (https://www.facs.org/quality-programs/trauma/quality/best-practices-guidelines)

Published by: American College of Surgeons **Last published:** 2022

Perinatal depression: preventive interventions (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics)

Published by: US Preventive Services Task Force **Last published:** 2019

Recommendations on screening for depression in adults (https://canadiantaskforce.ca/guidelines/all-guidelines)

Published by: Canadian Task Force on Preventive Health Care **Last published:** 2013

Treatment guidelines

United Kingdom

Perinatal mental health conditions (https://www.sign.ac.uk/our-guidelines/perinatal-mental-health-conditions)

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2023

Depression in adults: treatment and management (https://www.nice.org.uk/guidance/ng222)

Published by: National Institute for Health and Care Excellence **Last published:** 2022

Rehabilitation for adults with complex psychosis (https://www.nice.org.uk/guidance/ng181)

Published by: National Institute for Health and Care Excellence **Last published:** 2020

British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum 2017 (https://www.bap.org.uk/guidelines)

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

Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines (https://www.bap.org.uk/guidelines)

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

Europe

Improving mental health care in depression: a call for action (https://www.europsy.net/guidance-papers)

Published by: European Psychiatric Association **Last published:** 2023

International

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders (https://www.who.int/publications/i/item/9789240084278)

Published by: World Health Organization **Last published:** 2023

Guidelines for biological treatment of unipolar depressive disorders, part 2: maintenance treatment of major depressive disorder - update 2015 (https://wfsbp.org/educational-activities/treatment-cuidelines-and-consensus-paper)

Published by: World Federation of Societies of Biological Psychiatry **Last published:** 2015

Guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders (https://wfsbp.org/educational-activities/treatment-cuidelines-and-consensus-paper)

Published by: World Federation of Societies of Biological Psychiatry **Last published:** 2013

North America

Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder (https://www.acponline.org/clinical-information/clinical-guidelines-recommendations)

Published by: American College of Physicians **Last published:** 2023 (reaffirmed 2025)

Clinical guidelines for the management of adults with major depressive disorder (https://journals.sagepub.com/doi/10.1177/07067437241245384)

Published by: Canadian Network for Mood and Anxiety Treatments **Last published:** 2023

Treatment and management of mental health conditions during pregnancy and postpartum (https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2023

VA/DoD clinical practice guideline for the management of major depressive disorder (https://www.healthquality.va.gov/guidelines/MH/mdd)

Published by: US Department of Veterans Affairs; Department of Defense **Last published:** 2022

Depression, adult in primary care (https://www.icsi.org/guideline)

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

The CANMAT task force recommendations for mood disorders and comorbid conditions: diagnostic, assessment, and treatment principles (https://www.canmat.org/resources/)

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

Practice guideline for the treatment of patients with major depressive disorder (https://psychiatryonline.org/guidelines)

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

Oceania

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (https://www.ranzcp.org/clinical-guidelines-publications/in-focus-topics/mood-disorders)

Published by: The Royal Australian and New Zealand College of Psychiatrists **Last published:** 2024

Online resources

1. WHO: Global Health Estimates (https://www.who.int/data/global-health-estimates) *(external link)*
2. IHME: Global Burden of Disease (GBD) (https://www.healthdata.org/research-analysis/gbd) *(external link)*
3. Edinburgh Postnatal Depression Scale (https://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf) *(external link)*
4. Cornell Scale For Depression in Dementia (https://cgatoolkit.ca/Uploads/ContentDocuments/cornell_scale_depression.pdf) *(external link)*
5. UK Teratology Information Service (http://www.uktis.org) *(external link)*
6. STOPP-START (https://www.cgakit.com/m-2-stopp-start) *(external link)*

EVIDENCE TABLES

Evidence tables

What are the effects of cognitive behavioural therapy (CBT) versus second-generation antidepressants (e.g., selective serotonin-reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors) in adults with major depressive disorder?[170]

This table is a summary of the analysis reported in a systematic review that focuses on the above important clinical question.

View the full source systematic review (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5623437)

Evidence B *	Confidence in the evidence is moderate or low to moderate where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes.

Population: Adults with major depressive disorder

Intervention: CBT

Comparison: Second-generation antidepressants (e.g., selective serotonin-reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors)

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Response to treatment	No statistically significant difference	Moderate

Note

The reviewers of the systematic review (view the full source systematic review above) used ‘response to treatment' as defined in the individual studies, but report that most commonly this was presented as a 50% reduction of symptoms on a depression rating scale (e.g., Hamilton Depression Scale).

What are the effects of St John's Wort in adults with major depressive disorder compared with antidepressants?[456]

This table is a summary of the analysis reported in a systematic review that focuses on the above important clinical question.

View the full source systematic review (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5010734)

Evidence C * — Confidence in the evidence is very low or low where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Adults with major depressive disorder
Intervention: St John's Wort
Comparison: Antidepressant

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Depression, number of treatment responders	No statistically significant difference	Moderate
Depression scale score	No statistically significant difference	Moderate
Depression remission	No statistically significant difference	Low
Depression relapse	No statistically significant difference	Very Low
Quality of life: mental	No statistically significant difference	Very Low
Quality of life: physical	Favours intervention	Very Low
Number of patients with adverse events	Occurs more commonly with antidepressants compared with St John's Wort (favours intervention)	Moderate
Serious adverse events	No statistically significant difference	Low
Gastrointestinal/metabolic/ nutritional adverse events	Occurs more commonly with antidepressants compared with St John's Wort (favours intervention)	Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Neurological/nervous system adverse events	Occurs more commonly with antidepressants compared with St John's Wort (favours intervention)	Low
Skin/musculoskeletal adverse events	No statistically significant difference	Low
Respiratory/infectious adverse events	No statistically significant difference	Very Low
Other organ system (eye, ear, liver, renal, reproductive) adverse events	No statistically significant difference	Low
Cardiovascular adverse events	No statistically significant difference	Low
Psychiatric adverse events	Occurs more commonly with antidepressants compared with St John's Wort (favours intervention)	Very Low
Sexual dysfunction adverse events	Occurs more commonly with antidepressants compared with St John's Wort (favours intervention)	Low

Note

- The reviewers of the systematic review (view the full source systematic review above) concluded that St John's Wort is similarly effective when compared with antidepressants.
- Fewer adverse events occurred in the gastrointestinal, neurological, and psychiatric functioning with St John's Wort when compared with antidepressants.
- Only studies with a treatment duration of ≥4 weeks were included.

What are the effects of St John's Wort in adults with major depressive disorder compared with placebo?[456]#

This table is a summary of the analysis reported in a systematic review that focuses on the above important clinical question.

View the full source systematic review (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5010734)

Evidence C * Confidence in the evidence is very low or low where GRADE has been performed and the intervention may be more effective/beneficial than the comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Adults with major depressive disorder
Intervention: St John's Wort
Comparison: Placebo

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Depression, number of treatment responders	Favours intervention	Moderate
Depression scale score	Favours intervention	Moderate
Depression remission	No statistically significant difference	Low
Depression relapse	No statistically significant difference	Very Low
Quality of life: mental	Favours intervention	Low
Quality of life: physical	No statistically significant difference	Very Low
Number of patients with adverse events	No statistically significant difference	Moderate
Serious adverse events	No statistically significant difference	Moderate
Gastrointestinal/metabolic/ nutritional adverse events	No statistically significant difference	Low
Neurological/nervous system adverse events	Occurs more commonly with St John's Wort compared with placebo (favours comparison)	Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Skin/musculoskeletal adverse events	No statistically significant difference	Very Low
Photosensitivity	No statistically significant difference	Low
Respiratory/infectious adverse events	No statistically significant difference	Low
Other organ system (eye, ear, liver, renal, reproductive) adverse events	Occurs more commonly with St John's Wort compared with placebo (favours comparison)	Low
Cardiovascular adverse events	No statistically significant difference	Very Low
Psychiatric adverse events	No statistically significant difference	Very Low
Sexual dysfunction adverse events	No statistically significant difference	Very Low

Note

- The reviewers of the systematic review (view the full source systematic review above) concluded that St John's Wort is effective in treating major depressive disorder when compared with placebo.
- People experienced adverse events related to the nervous system, eye, ear, liver, renal, and reproductive organ systems with St John's Wort when compared with placebo.
- Only studies with a treatment duration of ≥4 weeks were included.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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// Acknowledgements:

Dr Dean F. MacKinnon would like to gratefully acknowledge Dr Roger S. McIntyre, Dr Tonya Fancher, and Dr Richard Kravitz, the previous contributors to this topic.
DISCLOSURES: RSM has received research funds from Stanley Medical Research Institute and National Alliance for Research on Schizophrenia and Depression (NARSAD). RSM is on the advisory board for AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen-Ortho, Solvay/Wyeth, Eli Lilly, Organon, Lundbeck, Biovail, Pfizer, Shire, and Schering-Plough. RSM is on the Speakers Bureau for Janssen-Ortho, AstraZeneca, Eli Lilly, Lundbeck, Biovail, and Wyeth. RSM has received research grants from Eli Lilly, Janssen-Ortho, Shire, and AstraZeneca. RSM has received travel funds from Bristol-Myers Squibb. TF declares that she has no competing interests. RK has received research grants from Pfizer on non-depression-related topics.

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DISCLOSURES: CD has been reimbursed by Novartis for participating in an educational event.

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DISCLOSURES: EKF declares that she has no competing interests.