BMJ Best Practice

Depression in children

Straight to the point of care

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Summary

Depression in children is characterised by sad or irritable mood, anhedonia, decreased capacity to have fun, decreased self-esteem, sleep disturbance, social withdrawal or impaired social relationships, and impaired school performance.

At-risk children should be screened for depression. It is crucial to make an accurate diagnosis, based on a comprehensive assessment and review of the history, with input from multiple sources.

The safety of the child and others, and the duration and severity of depression, need to be evaluated carefully to help determine the appropriate level of care and treatment modality. Treatment is typically with active monitoring, specific psychotherapies, antidepressants, or a combination of these therapies.

There is an increased risk for school disengagement, substance use disorders, suicide attempts, and completed suicide. Suicidality needs to be assessed at each healthcare encounter.

Following recovery, relapse or recurrence rate is high in the absence of continuation treatment.

Definition

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition, text revision (DSM-5-TR) categorises depressive disorders into the following categories: major depressive disorder (MDD), persistent depressive disorder, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder.[1] This topic focuses on MDD and persistent depressive disorder. MDD in children is a more severe form of depressive disorder, and is characterised by at least 5 depressive symptoms, with 3 levels of severity: mild, moderate, and severe. Persistent depressive disorder is a more chronic form of depressive disorder, which is characterised by a chronic sad or irritable mood, lasting for at least 1 year, with 2 or more additional depressive symptoms.

Epidemiology

The prevalence rates of childhood depression vary somewhat, depending on the sample and period assessed.

In the US, data from the 2016 National Survey of Children's Health suggests that 3.2% of children aged 3 to 17 years have a current diagnosis of depression.[3] In adolescents, the 12-month prevalence rises to approximately 8%.[4] Before puberty, girls and boys have similar rates of depression, but a gender difference emerges around early adolescence from the age of 12 onwards, when the diagnosis becomes more common in girls.[4] Depression becomes more than twice as prevalent in young women than in men by mid-adolescence to early adulthood (aged 14-25 years).[4] [5] The ages of 13 to 18 represent a key period for depression onset in both boys and girls; depression rates rise substantially for both sexes during this time.[3] [6] The majority of depressive illnesses in adults can be traced back to their origins in adolescence.[7]

There is some evidence to suggest an increase of major depressive disorder in certain areas within the past two decades; in Australia, a national survey found an approximately 50% increase in community prevalence rates between 1998 and 2014.[8] In the UK, the number of 12- to 17-year-olds prescribed antidepressants more than doubled between 2005 and 2017 (although antidepressant prescriptions decreased slightly overall for children aged 5-11 between 1999 and 2017).[9] It is unclear to what extent this represents a change in depression rates, or difference in diagnosis and treatment, during this period.

The presence of poverty has been associated with an increased risk of children requiring treatment for depression.[3] [9] [10] Depressive disorders may be higher in indigenous children and in children with chronic medical illness.[11] [12]

Depression in childhood is frequently associated with psychiatric and behavioural comorbidities. In the US, around 73.8% of children aged 3 to 17 years with depression also have anxiety, and 47.2% have co-occurring behavioural problems.[3]

Aetiology

Childhood depression is likely to be caused by both genetic and environmental factors, and by their interactions. It is estimated that up to 40% of variance can be explained by genetic factors, and the remaining variances can be explained by environmental factors and by the interactions between genetic factors and the environment.[13] [14] Life stress has been strongly associated with risk of depression, especially in girls.[15]

Pathophysiology

Exactly how genetic and environmental factors lead to the clinical manifestation of a depressive disorder is not fully understood. It is suspected that the process is complex and multifactorial. The pathophysiology of childhood depression is less well understood than that of adult depression. Fewer studies have been conducted in the paediatric population, and some of the adult findings have not been demonstrated in childhood depression. Although in adults with depression cortisol hypersecretion is a consistent finding, the relationship between cortisol levels in childhood depression is less clear and in places contradictory.[16] Increased morning cortisol in youth at risk for depression predicts onset of depression.[17] There is some evidence to suggest that young people who develop depression in adolescence have higher than typical levels of cortisol, but that those who develop symptoms earlier may have unusually low levels, suggesting the possibility of hypothalamic-pituitary-adrenal axis blunting over time in response to ongoing depression.[18]

There is also evidence indicating the dysregulation of the central serotonergic systems in childhood depression. Pre-pubertal depressed children were found to have attenuated cortisol but increased prolactin secretion responding to L-5-hydroxytryptophan challenge.[19] It is suggested that dysregulation of the central serotonergic system could lead to an impaired stress and emotional response, decreased impulse control, and emotional dysregulation.[20] [21]

Studies in adults with depression have indicated several sleep abnormalities through polysomnographic studies, including reduced sleep continuity, reduced slow-wave sleep, shortened rapid eye movement (REM) latency, and increased REM density. However, sleep studies in children and adolescents with depression have been inconsistent. Some studies indicate that depressed children and adolescent inpatients have sleep continuity disturbances and an increase in REM pressure (shortened REM latency and increased REM sleep %), but not disturbances in slow-wave sleep.[22] [23] [24] [25] [26] The results in outpatients have been mixed.[27] [28] [29]

The disruption in the motivation-and-reward neurological pathway has also been indicated in paediatric depression.[30] There is evidence of the involvement of the glutamatergic system in the pathophysiology of depressive disorders.[31] Imaging studies have found volumetric and functional disruptions in multiple brain regions and pathways (e.g., in the amygdala, anterior cingulate, prefrontal cortex) that are important in emotional regulation, stress response, motivation, behavioural inhibition, and the manifestation of depressive symptoms.[32] [33] [34] [35]

Classification

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

Categorises depressive disorders into the following categories: major depressive disorder (MDD), persistent depressive disorder, disruptive mood dysregulation disorder (DMDD), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. This topic focuses on MDD and persistent depressive disorder.

MDD

- Similar to adults, characterised by at least 5 depressive symptoms, occurring over the same 2-week period.
- Depressive symptoms include: depressed mood, diminished interest or pleasure, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, diminished concentration and recurrent thoughts of death, suicidal ideation or suicide attempt.
- Children and adolescents may have irritability instead of depression as one of the primary mood symptoms.
- A child needs to have at least one of the key symptoms (sad or irritable mood, anhedonia), associated with a significant impairment in functioning in multiple areas, such as school or socially.

Persistent depressive disorder

- Represents a consolidation of the diagnoses of chronic MDD and dysthymic disorder.
- A more chronic form of depressive disorder than MDD.

- Characterised by a chronic sad or irritable mood that lasts for at least 1 year (must be 2 years in adults).
- Must also have at least 2 of the following symptoms: disturbed appetite, insomnia or hypersomnia, decreased energy level, low self-esteem, poor concentration, and feelings of hopelessness.
- During the 1-year period, a child never has been without the minimum 3 symptoms for more than 2 consecutive months.

International classification of diseases, 11th revision (ICD-11)[2]

The ICD-11 is overall consistent with the DSM-5-TR criteria. The ICD-11 threshold for 'depressive episode' is the same, with at least five of the characteristic symptoms: depressed mood (or irritability in children), diminished interest or pleasure in activities, poor concentration, low self-worth, recurrent thoughts of death, disrupted sleep, change in appetite, psychomotor agitation, or retardation and fatigue; in addition, ICD-11 includes an extra symptom of hopelessness that is not included in the DSM-5-TR.

Case history

Case history #1

A 15-year-old girl, at a private school, presents with poor concentration. She lives with her biological mother and a 13-year-old sister. Her mother describes her as an outgoing and straight-A student until about 4 months ago. Her grades have slipped from As to Cs, and she has been feeling sad and irritable. She has started avoiding her friends, and has been worrying about her appearance and her grades. She states that she feels dumb, and that her classmates don't like her. Recently, she started to think that life was not worth living, and wished she would fall asleep and never wake up. Her boyfriend broke up with her about 3 months ago. The last time she felt this sad was 5 years ago when her parents divorced.

Case history #2

A 9-year-old boy presents with a change in his behaviour over the past 6 weeks, from being an outgoing child who loved school to frequently complaining of stomach aches and refusing to go to school. He lives with his biological parents and a 5-year-old sister. He is attending a local school. His parents say that he has been unkind to his 5-year-old sister, and frequently screams at her. He used to like to play outside after school, but recently has stayed in his room a lot and played video games. He cannot identify any precipitants, but his parents recall that his mother was hospitalised for surgery about 3 months ago.

Other presentations

Depression in children and adolescents may sometimes present as 'acting out', aggression, and defiance. Depression in younger children can present as somatic complaints and school refusal. Young people with a chronic medical illness may present with decreased concern about their medical illness and/or decreased compliance with medical treatment. Careful interviews with both the child and the parents are important to discover potential causes of the presentation, other depressive symptoms, and other concurrent conditions (both medical and psychiatric) that may exacerbate the depression.

Approach

Adolescent and pre-adolescent depressive disorders are clinical diagnoses, based on a comprehensive diagnostic evaluation of history and presenting symptoms. It is crucial to make an accurate diagnosis, with input from multiple sources including, but not limited to, the child, parents, and school (teachers, counsellors).

Symptoms and signs are identified by parents or teachers, or less commonly self-reported by the child or adolescent. The pathway to the physician is usually via the parent, although it may be on the recommendation of the school. Alternatively, the diagnosis may be made following screening. The author's view is that children and adolescents with risk factors for depressive illness who are seen at primary care settings should be screened for depressive disorder. Screening of children and adolescents with risk factors for major depressive disorder is also recommended in the emergency department setting.[63] Annual universal screening in a primary care setting is recommended for all children aged 12 years and older, even in the absence of specific risk factors, according to US-based guidance.[64] This approach is endorsed by the US Preventive Services Task Force (USPSTF).[65] At present, the USPSTF does not recommend screening for depression in children aged 11 years or younger, based on insufficient evidence of net benefit. However, note that in children in this age group, early identification can facilitate early intervention.[66] Children who come into contact with psychiatric services always need to be screened for depression, because depression is highly comorbid with other psychiatric disorders.[67] Depression rating scales may support initial diagnosis of depression, and may also facilitate measurement of response to treatment over time ('measurement-based treatment').[66] See 'Screening ' for details on recommended screening instruments (depression rating scales) in different age groups.

A safety assessment, including review of thoughts of suicide and self-harm, should be completed by the clinician at the first clinical encounter, and at all subsequent encounters.[64] [68] In adolescents, asking about suicidality should typically take place in a confidential manner, without carers present, given that young people may be reluctant to report suicidal ideation in the company of carers.[68] The American Academy of Pediatrics (AAP) recommends the use of a brief suicide safety assessment (BSSA) for all patients disclosing suicidal ideation, in order to further explore their personal risk and protective factors. Note that the BSSA is different from the initial screening tool, which simply identifies risk.[69] It is imperative to ask about access to lethal means (firearms, medicines, illicit substances, knives, ropes) when suicidal ideation or a plan is disclosed, followed by risk-tailored counselling and mitigation.[68] [70] A positive screening result for suicidal ideation should be followed safety planning, an intervention that encompasses helping the patient identify their risk factors for suicidal ideation as well as a series of supports that they can draw on to reduce their risk of self-harm. Children and adolescents who are depressed with severe suicidality without being able to maintain safety, or with significant psychosis, require urgent referral to the accident and emergency department.

See: Suicide risk mitigation .

Other safety risks to explore include risk-taking behaviour and impulsivity. Clinicians should explore exposure to childhood adversities; if there is suspicion of abuse or neglect, collateral history may be needed, plus referral to local childhood welfare authorities according to the location of practice.[66] Two basic questions may help guide a safeguarding assessment: (1) Is the patient at current risk? (2) Are the patient and family able to adhere to recommendations regarding supervision, safeguarding, and follow-up care? The answers to these questions will help to guide the appropriate level and intensity of care.[66]

There is no specific test for childhood depression. Hypothyroidism, anaemia, autoimmune diseases, vitamin deficiencies, and infectious mononucleosis could cause symptoms of depression. Depression risk is also increased in inflammatory bowel disease, asthma, and epilepsy, and with use of medications that are depressogenic, including corticosteroids. A baseline full blood count (FBC) with differential and thyroid function tests should be performed to exclude medical causes of depression, particularly if other symptoms of these disorders are present, or if the child is at risk for these disorders.

History

Both the child and parent/guardian should be interviewed, either separately or together or both, as developmentally and clinically indicated.[66] For older children and for adolescents, it is good practice to see them on their own for at least part of the consultation, and this may encourage young people to describe symptoms that they are reluctant to mention in the presence of an accompanying adult. Screening should be completed by direct clinician interview, in addition to screening instruments.[64] A collateral history (e.g., from teachers, primary care, child agency workers, other family members etc, as appropriate, and ensuring that the appropriate consent has been obtained) may be beneficial.[66]

For adolescents in particular, interviewing them first may improve engagement. A careful investigation of the following points is important to formulate a diagnosis:

- The length of time for which depressive symptoms have been present
- Potential precipitants
- Any change of functioning.

Adolescent and pre-adolescent depression is often precipitated by the loss of loved ones (including pets), loss of peer support due to relocation, and conflicts with peers and/or parents. A careful review of the following will help to exclude differential diagnoses and formulate the treatment plan:

- Developmental history
- Medical history
- Presence of comorbid psychiatric disorders, substance use or misuse
- Family history of psychiatric illness, particularly depression and bipolar disorder.

Risk factors that are strongly associated with depression include a family history of depression, other parental psychopathology, stress or trauma, female sex, sexual minority (lesbian, gay, bisexual, transgender, and questioning) status, a personal history of other psychiatric disorders (e.g., anxiety or conduct disorder) or a chronic medical condition, postnatal status, neighbourhood and social instability, and the use of immunosuppressive medications.

Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR): criteria for major depressive disorder

To diagnose major depressive disorder (MDD), a child needs to have at least 5 of the following 9 symptoms, which indicate a significant change from his or her baseline presentation, during a same 2-week period, with at least one symptom being either depressed or irritable mood or anhedonia:[1]

- Depressed or irritable mood
- Decreased interest or lack of enjoyment
- Decreased concentration or indecision
- Insomnia or hypersomnia

- Change of appetite or change of weight
- Excessive fatigue
- Feelings of worthlessness or excessive guilt
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a specific suicide plan, or a suicide attempt.
- Psychomotor agitation or retardation.

In addition, these symptoms must cause significant functional impairments in school, social settings, and/or family. They are not better accounted for by a grief reaction, and are not due to a substance or to a medical illness. There should not be a history of manic or hypomanic episodes.

The International Classification of Diseases, 11th revision (ICD-11) is overall consistent with the DSM-5-TR criteria. The ICD-11 threshold for 'depressive episode' is the same: at least five symptoms, but it is out of a list of ten instead of nine in the DSM-5-TR. The additional symptom is 'hopelessness'.[2]

MDD can be classified according to how many episodes have occurred.

- MDD, single episode: the presence of 1 major depressive episode, not part of schizoaffective disorder or superimposed on a psychotic disorder; no history of a manic episode or a hypomanic episode
- MDD, recurrent: criteria are the same as MDD, single episode, but with at least 2 major depressive episodes.

MDD is also classified according to 3 levels of severity:

- Mild
- Moderate
- Severe, with or without psychotic features.

Exact features for each of these severity levels are not clearly defined. Individual physicians make a judgement of the severity of the depressive disorder, based on global functional impairment ratings and the severity and number of symptoms present. However, if admission to hospital is required for treatment of MDD, it is classified as severe. For the severe form with psychotic features, the psychotic features could be either mood-congruent or mood-incongruent, depending on whether the content of the delusions or hallucinations is consistent or inconsistent with depressive themes.

There are 9 specifiers:

- With anxious distress
- With mixed features
- With catatonia
- With melancholic features
- With atypical features
- With mood-congruent psychotic features
- With mood-incongruent psychotic features
- With peripartum onset
- With seasonal pattern.

Diagnostic and statistical manual of mental disorders, fifth edition, text revision (DSM-5-TR): criteria for persistent depressive disorder

A child needs to have at least 3 of the following symptoms, which occur most of the day, more days than not, and for at least 1 year, and sad or irritable mood must be one of the symptoms:[1]

- Sad or irritable mood
- Increased or decreased appetite
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self-esteem
- Poor concentration or indecision
- Feelings of hopelessness.

In addition, the following criteria need to be met to make a persistent depressive disorder diagnosis:

- During the year, the child has never been without sad or irritable mood and 2 other symptoms for >2 months at a time
- These symptoms cause significant distress or impairment in multiple areas of functioning
- There has never been a manic or hypomanic episode, or symptoms meeting the criteria for cyclothymic disorder
- The symptoms are not caused by a substance medical condition
- The symptoms are not better explained by schizoaffective disorder or other psychotic disorder.

Presenting symptoms

Both the child and the parents should be asked about specific depressive symptoms, based on the DSM-5-TR diagnostic criteria. Core symptoms are sad and/or irritable mood and diminished enjoyment of activities/anhedonia. Associated symptoms include decreased concentration and school performance, a change of appetite, difficulties with sleep, low self-esteem, hopelessness, excessive guilt, and suicidal thoughts. A common sign in a depressed child is social withdrawal or changes in social relationships, as most anxious children remain socially motivated. Although not a DSM-5-TR diagnostic criterion, excessive somatic complaints may also be common, especially in the younger depressed child. Both self- and parent-rating scales and clinician-rating scales may be helpful in eliciting symptoms. These scales can be used throughout treatment to more effectively monitor improvement or worsening of symptoms.

In addition, clinicians need to review the child for manic and hypomanic symptoms such as elevated mood, decreased need for sleep, and grandiosity, as well reviewing the family history, to exclude the potential possibility of a bipolar disorder. Adults with bipolar disorder often report that their initial symptoms were of a depressive disorder. All children and adolescents presenting with depression should be screened for manic symptoms.

Sometimes, depressed children will also experience hallucinations or delusional thoughts about worthlessness or guilt as part of the depressed mood syndrome. While this does not mean the child has a psychotic disorder, it is important to note the presence of these factors, ensure they improve with treatment for depression, and consider this when developing a treatment plan.

Depression frequently co-occurs with substance use disorders during adolescence. In addition, some substances are known to cause depressive symptoms.[57] [58] According to the DSM-5-TR diagnostic

criteria, a diagnosis of MDD or persistent depressive disorder should not be made if the symptoms are thought to be related to the direct effect of a substance or a medication.

It is important to exclude a normal bereavement response as the cause of the presentation. Although symptoms of depression may increase the risk of children and young people self-medicating with various substances, it is also important to exclude the possibility that the presentation is a direct effect of a substance.

Clinicians should also assess for the presence of the following common comorbid mental health conditions, which may affect the diagnosis and management of the depressive disorder:[64]

- Anxiety disorders
- Attention-deficit hyperactivity disorder
- Autism spectrum disorder
- Physical abuse and trauma.

Impairment

An assessment of functional impairment resulting from the current depressive symptoms needs to be included. Depressive symptoms need to cause significant impairment in one or more areas of functioning (e.g., school, home, social settings) to meet DSM-5-TR criteria for MDD or persistent depressive disorder. Information regarding the severity of depressive symptoms and functioning impairment will guide the treatment approach.

Examination

There are no specific physical examination findings for depression, but a physical examination is helpful in excluding medical causes of depression. Various medical causes include:

- Infectious mononucleosis
- Vitamin deficiencies
- Anaemia
- Substance use disorder
- Thyroid dysfunction.

In many cases, symptoms of these conditions may not be easily differentiated from symptoms of depression (e.g., lack of energy, poor appetite, hypersomnia), which should be kept in mind during the physical examination and subsequent work-up. With increasing rates of juvenile obesity, which in itself can be comorbid with depression, there is an increase of micronutrient deficiency (e.g., vitamin B12, iron, folate, vitamin D).[71]

A mental status examination of a child's attention, affect, speech, motor activity, thought process, thought content, suicidal and homicidal thoughts, hallucinations, delusions, insight, and judgement will help to determine an appropriate level of care and treatment approach. Psychomotor agitation or retardation may be noted.

Investigations

A work-up for reversible causes of depression should be considered standard practice. The most common baseline tests include:

- FBC (with differential)
- Serum thyroid-stimulating hormone and free thyroxine
- Urine drug screen
- Screening for vitamin deficiencies, especially B12, folate, and vitamin D.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Positive family history of depression, other parental psychopathology, history of stressful life events or trauma, female sex, postnatal status, comorbid psychiatric disorders or chronic medical illnesses, and neighbourhood and social instability are important risk factors for depression.

sad and/or irritable mood (common)

- A child needs to have either sad/irritable mood or anhedonia as one of the symptoms to meet the DSM-5-TR diagnostic criteria for major depressive disorder (MDD).
- Irritable mood could be as common as sad mood, but typically does not present without the presence of sad mood concurrently.
- To meet DSM-5-TR MDD episode criteria, the sad/irritable mood or anhedonia must be present most of the day, almost every day, for at least 2 weeks, and co-exist with 4 other depressive symptoms.
- To diagnose persistent depressive disorder (dysthymia) in children or young people, a sad or irritable mood needs to be present for at least 1 year, and is typically of lesser intensity than during a depressive episode.

decreased interest or lack of enjoyment (common)

- A child needs to have either sad/irritable mood or anhedonia as one of the symptoms to meet the DSM-5-TR diagnostic criteria for MDD.

significant functional impairment (common)

- Depressive symptoms need to cause significant impairment in one or more areas of functioning (e.g., school, home, social settings) to meet DSM-5-TR criteria for major depressive disorder or persistent depressive disorder (dysthymia).

no evidence of a manic or hypomanic episode (common)

- There should not be a history of manic or hypomanic episode.

no history of recent bereavement (common)

- There are overlapping symptoms between major depressive disorder and bereavement.

Other diagnostic factors

decreased concentration or indecision (common)

- One of the DSM-5-TR listed depressive symptoms for major depressive disorder and persistent depressive disorder (dysthymia).
- Frequently related to decreased school performance. The poor school performance should not relate to lack of ability to do the work.
- During summer months, when school is out, may manifest as taking longer to read or remember what was read, not being able to follow a TV programme, or having to ask parents to make choices.
- If a child has a history of poor concentration (e.g., with ADHD), there must be a worsening with the onset of mood disturbance for this to be counted as a depressive symptom. It must be a change from baseline.

insomnia or hypersomnia (common)

- One of the DSM-5-TR listed depressive symptoms for major depressive disorder and persistent depressive disorder (dysthymia).
- Insomnia may be initial, middle, or terminal. Initial and middle insomnia are more common forms of insomnia in child depression.
- Hypersomnia usually presents more commonly among adolescents than among young children.

change of appetite or weight (common)

- One of the DSM-5-TR listed depressive symptoms for major depressive disorder and persistent depressive disorder (dysthymia).
- Appetite could decrease or increase, with or without weight change.

excessive fatigue (common)

- One of the DSM-5-TR listed depressive symptoms for major depressive disorder and persistent depressive disorder (dysthymia).

feelings of worthlessness or excessive guilt (common)

- One of the DSM-5-TR listed depressive symptoms for major depressive disorder. A child may have negative self-perception or excessive guilt.
- Decreased self-esteem is among the most common depressive symptoms in children.

feelings of hopelessness (common)

- One of the DSM-5-TR listed depressive symptoms for persistent depressive disorder (dysthymia).

psychomotor agitation or retardation (common)

- One of the DSM-5-TR listed depressive symptoms for major depressive disorder.

somatic complaints (common)

- Although it is not a DSM-5-TR diagnostic criterion for major depressive disorder, excessive somatic complaints may be common in younger depressed children, most commonly headaches or abdominal pain.

social withdrawal or change of friends (common)

- A common sign of a depressed child.

recurrent thoughts of death or suicidal ideation and self-harm (uncommon)

- One of the DSM-5-TR listed depressive symptoms for major depressive disorder. Various degrees of suicidality may present, ranging from morbid thoughts of death to suicidal thoughts with plans and intent.
- The milder forms of suicidality are more common.

increased substance use (uncommon)

- Depression frequently co-occurs with substance use problems and disorders during adolescence.
- In addition, some substances are known to cause depressive symptoms.[57] [58] According to the DSM-5-TR diagnostic criteria, a diagnosis of major depressive disorder or persistent depressive disorder (dysthymia) should not be made if the symptoms are thought to be related to the direct effect of a substance or a medication.

Risk factors

Strong

positive family history of depression

- Family loading of depression is the single most significant predictor for the development of a depressive disorder.[36]
- Based on twin and adoption studies, genetic factors are estimated to account for up to 40% of variance in depression. Evidence also indicates that the hereditability of depression is higher in girls than in boys in adolescence.[37]
- Children with depressed parents are 2 to 4 times more likely to have depression.[38]
- Both maternal and paternal depression have been linked to depression and other psychiatric disorders in children.[39] [40] [41] This impacts children through both genetic and environmental effects, and is associated with more marital conflict, poor parenting, and decreased support.[42] [43]

other parental psychopathology

- In addition to parental depression, high rates of other parental psychopathology (e.g., alcohol use disorder, substance use disorders, suicidal behaviours, anxiety disorders) have been found in children and adolescents with depression.[44] [45]

personal history of other psychiatric disorders (e.g., anxiety)

- Depression in childhood is frequently associated with psychiatric and behavioural comorbidities. In the US, around 73.8% of children aged 3 to 17 with depression also have anxiety, and 47.2% have co-occurring behavioural problems.[3]

stress or trauma

- Stress and trauma trigger a depressive episode in children and adults. Genetic evidence has illustrated the interplay between stress, trauma, and genetic vulnerability.[46]

female sex

- Increases susceptibility to depression, particularly during adolescence.
- By mid-adolescence, the prevalence rate of depression in females is almost twice that of depression in males.[5]

sexual minority status

- Most lesbian, gay, bisexual, transgender, and questioning (LGBTQ) youth are quite resilient and emerge from adolescence as healthy adults. However, the effects of homophobia and heterosexism can contribute to health disparities in mental health between LGBTQ and other youth, with higher rates of depression and suicidal ideation.[47] LGBTQ youth also have higher rates of abuse that account for some of this disparity.[48] [49]

personal history of chronic medical illness

- Depression rates are higher among chronically ill children.
- Up to 26% of children with diabetes mellitus have depression, and up to 30% of children with asthma have a depressive disorder.[50] [51]

postnatal status

- About 10% to 20% of women giving birth develop postnatal depression.[52] [53] Up to 48% of adolescent mothers in the US have been found to have depressive symptoms (surveyed at a mean of 17 months postnatal).[54] [55]

neighbourhood and social instability

- Neighbourhood instability, violence, and poor resources provided by the school and neighbourhood have been associated with the development of childhood depression and other psychopathologies.[44] [56]

immunosuppressive medications (e.g., corticosteroids, interferon)

- Both corticosteroids and interferon have documented depression as adverse effects.

substance use problems/disorders

- Depression frequently co-occurs with substance use problems/disorders during adolescence. There is evidence that substance use problems may increase the risk of developing depressive disorders, and some substances are known to cause depressive symptoms.[57] [58]

Investigations

1st test to order

Test	Result
clinical diagnosis • Adolescent and pre-adolescent depressive disorders are clinical diagnoses, based on a comprehensive diagnostic evaluation of history and presenting symptoms. It is crucial to make an accurate diagnosis, with input from multiple sources including, but not limited to, the child, parents, and school (teachers, counsellors).	**fulfils diagnostic criteria**

Other tests to consider

Test	Result
serum thyroid-stimulating hormone (TSH) and free thyroxine (T4) • Baseline assessment to exclude thyroid dysfunction. • Primary hypothyroidism: elevated TSH; free T4 may be low. • Hyperthyroidism: suppressed TSH; elevated free T4.	**normal; excludes thyroid dysfunction**
full blood count with differential • Baseline assessment to exclude anaemia or other disorders. • Infectious mononucleosis: may show anaemia, reticulocytosis, lymphocytosis, atypical lymphocytes. • Iron deficiency: microcytic, hypochromic anaemia; low reticulocyte count. • Hypothyroidism: occasionally mild anaemia; macrocytosis. • Vitamin B12 deficiency: elevated mean corpuscular volume, low haematocrit.	**normal**
urine drug screen • Baseline assessment test.	**negative or positive for substance**
urine pregnancy test • Screen for pregnancy in females should also be completed.	**variable**
serum B12 and folate • Helpful in excluding medical causes of depression. With increasing rates of juvenile obesity, which in itself can be comorbid with depression, there is an increase of micronutrient deficiency.	**normal**
vitamin D level • Helpful in excluding medical causes of depression. With increasing rates of juvenile obesity, which in itself can be comorbid with depression, there is an increase of micronutrient deficiency.	**normal**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Bipolar disorder	• Clinical examination using the DSM-5-TR criteria establishes differentiating symptoms and signs. • Elevated mood, decreased need for sleep, inflated self-esteem or grandiosity, increased goal-directed activities, racing thoughts, pressured speech, and reckless pleasurable behaviour are all characteristics of hypomanic or manic episodes of a bipolar illness. A child, particularly an adolescent, who presents with a history or concurrent manic or hypomanic symptoms needs to be assessed carefully to exclude the possibility of a bipolar illness. • It is important to have a low index of suspicion for bipolar disorder even if the symptoms are subthreshold, given that bipolar disorder often presents in the depressed polarity.	• No differentiating test.
Anxiety disorder	• Clinical examination using the DSM-5-TR criteria establishes differentiating symptoms and signs. Dysphoria associated with anxiety will dissipate in the absence of an anxiogenic situation. • Anxiety disorders that meet diagnostic criteria will usually precede depressive symptoms. Anxiety disorders do not occur exclusively during a mood disorder; rather, symptoms of anxiety are present even in the absence of mood symptoms. • However, anxiety disorders are highly comorbid with depressive disorders, and assessment and management of both	• No differentiating test.

Condition	Differentiating signs / symptoms	Differentiating tests
	disorders will improve outcome.	
ADHD	• Clinical examination using the DSM-5-TR criteria establishes differentiating symptoms and signs. Mood changes due to ADHD can be either due to a side effect of stimulants, or demoralisation as a result of difficulties in school, with family, or with peers. • ADHD is diagnosed when full diagnostic criteria are met prior to age 12 years. In patients with ADHD only, poor concentration is a chronic symptom that precedes depressive symptoms. ADHD, however, is highly comorbid with depressive disorders, and assessment and management of both disorders will improve outcome.	• No differentiating test.
Substance use disorder	• Clinical examination using the DSM-5-TR criteria helps to establish differentiating symptoms and signs. • A substance use disorder may precede depressive symptoms or occur as a consequence of depression.	• Urine drug screen confirms concomitant use of substance.
Adjustment disorder with depressed mood	• A stressor always precedes the depressive symptoms. • In addition, the depressive symptoms should not meet full DSM-5-TR criteria for major depressive disorder.	• No differentiating test.
Bereavement	• A recent loss of a loved one always precedes the depressive symptoms.	• No differentiating test.
Acute stress disorder	• A recent exposure to a traumatic event, by experiencing, witnessing, or confronting, which causes intense fear, helplessness, or horror. • In addition, a child has dissociative symptoms, re-	• No differentiating test.

Condition	Differentiating signs / symptoms	Differentiating tests
	experiencing of the trauma, avoidance behaviour, and increased anxiety or arousal.	
Post-traumatic stress disorder	• Exposure to a traumatic event, by experiencing, witnessing, or confronting, which causes intense fear, helplessness, or horror for at least 1 month after the event. • In addition, the child has dissociative symptoms, re-experiencing of the trauma, avoidance behaviour, and increased anxiety or arousal.	• No differentiating test.
Oppositional defiant disorder	• Clinical examination using the DSM-5-TR criteria helps to establish differentiating symptoms and signs. • Irritability and defiance without other symptoms of depression, although epidemiological studies show that oppositional defiant disorder is a risk factor for eventual development of depression. • Behavioural problems are more chronic and present without concurrent mood symptoms.	• No differentiating test.
Anorexia nervosa	• Clinical examination using the DSM-5-TR criteria helps to establish differentiating symptoms and signs. Difficult to assess depressive status until nutritional and weight deficiencies are restored. • Additional symptoms, such as body image distortions and fear of gaining weight, occur without mood symptoms. • However, eating disorders and depression can be comorbid.	• No differentiating test.
Bulimia nervosa	• Clinical examination using the DSM-5-TR criteria helps to establish differentiating symptoms and signs. • Additional symptoms, such as body image distortions	• No differentiating test.

Condition	Differentiating signs / symptoms	Differentiating tests
	and over-eating, occur without mood symptoms. • However, eating disorders and depression can be comorbid.	
Thyroid dysfunction	• Hypothyroidism may be associated with weight gain and constipation. On examination there may be dry, coarse skin, goitre, bradycardia, facial puffiness, slow return of deep tendon reflexes, or tongue thickening. • Hyperthyroidism may be associated with weight loss, increased appetite, sweating, and nervousness. On examination there may be goitre, rapid return of deep tendon reflexes, or tremor.	• In primary hypothyroidism, thyroid-stimulating hormone (TSH) is elevated and free thyroxine (T4) is low. • In central hypothyroidism, TSH is inappropriately low or normal for the free T4 level, and free T4 is low. • In hyperthyroidism, TSH is suppressed and serum free T4 and/or triiodothyronine (T3) are elevated.
Anaemia	• May be associated with a history of poor nutrition, pallor, and prominent fatigue.	• Full blood count reveals low haemoglobin.
Infectious mononucleosis	• History of initial symptoms of fever, fatigue, malaise, pharyngitis, and cervical or generalised lymphadenopathy.	• Positive agglutination test (e.g., monospot) showing heterophile antibodies. • Serological test demonstrating Epstein-Barr virus-specific antibodies. • Full blood count with differential may demonstrate lymphocytosis, atypical lymphocytosis, anaemia, and reticulocytosis.
Vitamin deficiency	• May be associated with a history of poor nutrition, pallor, and prominent fatigue.	• Full blood count may reveal anaemia. • Blood levels of vitamins may be low. However, tests would only usually be performed if vitamin deficiency were considered a likely cause of symptoms. • Further specific tests of vitamin deficiency may be used to confirm deficiency.
Temporal lobe epilepsy	• History of recurrent and chronic focal seizures.	• Electroencephalogram reveals spikes or sharp waves in the temporal lobe area. This would only

Condition	Differentiating signs / symptoms	Differentiating tests
		usually be performed if temporal lobe epilepsy were considered a likely cause of symptoms.

Criteria

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

Categorises depressive disorders in children into the following categories: major depressive disorder (MDD), persistent depressive disorder, disruptive mood dysregulation disorder (DMDD), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. This topic focuses on MDD and persistent depressive disorder.

DSM-5-TR: criteria for major depressive#disorder[1]

To diagnose major depressive disorder, a child needs to have at least 5 of the following 9 symptoms, which indicate a significant change from his or her baseline presentation, during a same 2-week period, with at least one symptom being either depressed or irritable mood or anhedonia:

- Depressed or irritable mood
- Decreased interest or lack of enjoyment
- Decreased concentration or indecision
- Insomnia or hypersomnia
- Change of appetite or change of weight
- Excessive fatigue
- Feelings of worthlessness or excessive guilt
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a specific suicide plan, or a suicide attempt.
- Psychomotor agitation or retardation.

In addition, these symptoms must cause significant functional impairments in school, social settings, and/or family. They are not better accounted for by a grief reaction, and are not due to a substance or to a medical illness. There should not be a history of manic or hypomanic episodes.

The International Classification of Diseases, 11th revision (ICD-11) is overall consistent with the DSM-5-TR criteria. The ICD-11 threshold for ‘depressive episode’ is the same: at least five symptoms, but it is out of a list of ten instead of nine in the DSM-5-TR. The additional symptom is ‘hopelessness’.[2]

MDD can be classified according to how many episodes have occurred.

- MDD, single episode: the presence of 1 major depressive episode, not part of schizoaffective disorder or superimposed on a psychotic disorder; no history of a manic episode or a hypomanic episode.

- MDD, recurrent: criteria are the same as MDD, single episode, but with at least 2 major depressive episodes.

MDD is also classified according to 3 levels of severity:

- Mild
- Moderate
- Severe, with or without psychotic features.

Exact features for each of these severity levels are not clearly defined. Individual physicians make a judgement of the severity of the depressive disorder based on global functional impairment ratings, and the severity and number of symptoms present. However, if admission to hospital is required for treatment of MDD, it is classified as severe. For the severe form with psychotic features, the psychotic features could be either mood-congruent or mood-incongruent, depending on whether the content of the delusions or hallucinations is consistent or inconsistent with depressive themes.

There are 9 specifiers:

- With anxious distress
- With mixed features
- With catatonia
- With melancholic features
- With atypical features
- With mood-congruent psychotic features
- With mood-incongruent psychotic features
- With peripartum onset
- With seasonal pattern.

DSM-5-TR: criteria for persistent depressive disorder[1]

A child needs to have at least 3 of the following symptoms, which occur most of the day, more days than not, and for at least 1 year, and sad or irritable mood must be one of the symptoms:

- Sad or irritable mood
- Increased or decreased appetite
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self-esteem
- Poor concentration or indecision
- Feelings of hopelessness.

In addition, the following criteria need to be met to make a persistent depressive disorder diagnosis:

- During the year, the child has never been without sad or irritable mood and 2 other symptoms for >2 months at a time
- These symptoms cause significant distress or impairment in multiple areas of functioning
- There has never been a manic or hypomanic episode, or symptoms meeting the criteria for cyclothymic disorder
- The symptoms are not caused by a substance or medical condition
- The symptoms are not better explained by schizoaffective disorder or other psychotic disorder.

Screening

Screening for depression

Guidance on screening varies according to country of practice. The author's view is that children and adolescents with risk factors seen at primary care settings should be screened for major depressive disorder. Risk factors include:

- Family history of mood disorder
- History of trauma or recent trauma, including physical or sexual abuse or neglect
- Significant psychosocial stress (e.g., parental divorce, parental depression, severe parental medical illness, loss of a loved one including pets, conflict in peer or romantic relationships, conflict with parents)
- Poor performance in school
- Significant change of functioning
- Chronic or severe medical illness
- Certain medication treatment (e.g., corticosteroids, interferon)
- Recent history of giving birth.

Screening of children and adolescents with risk factors for major depressive disorder is also recommended in the emergency department setting.[63]

Annual universal screening for depression in a primary care setting is recommended for all children aged 12 years and older, even in the absence of specific risk factors, according to US-based guidance.[64] [65] This approach is endorsed by the US Preventive Services Task Force (USPSTF).[65] At present, the USPSTF does not recommend screening for depression in children aged 11 years or younger, based on insufficient evidence of net benefit. However, note that in children in this age group, early identification can facilitate early intervention.[66] Children who come into contact with psychiatric services always need to be screened for depression because depression is highly comorbid with other psychiatric disorders.[67]

Screening should be completed by direct clinician interview, in addition to one of the depression rating scales reviewed below.[64]

Reynolds Adolescent/Child Depression Scales (RADS/RCDS)

The RADS/RCDS is a child- and parent-report depression instrument with useful psychometric properties.[72] [73] It is an effective screening tool but probably not a good instrument for monitoring treatment outcomes.[74] It is available in multiple languages and is suitable for both children and adolescents. It is copyrighted, and therefore must be purchased from the publisher.

Mood and Feelings Questionnaire (MFQ)

The MFQ is a self-, parent-, and teacher-reported depression scale for children and adolescents.[75] It is a good screening tool and can be used in both clinical and research settings.[76] It can be accessed online for clinical or research use. [Duke University: Mood and Feelings Questionnaire] (https://devepi.duhs.duke.edu/measures/the-mood-and-feelings-questionnaire-mfq) A short version of the MFQ (MFQ-SF) was found to be sensitive in screening for major depressive disorder among youths aged 11-17 in a primary care setting.[77]

Beck Depression Inventory (BDI)

The BDI is a widely used adolescent self-rated depression scale with good psychometric properties.[74] [78] It is copyrighted, so must be purchased from the publisher.

Child Depression Inventory (CDI)

The CDI is a 27-item, self-rated assessment of depression and/or dysthymic disorder symptoms.[79] Items are grouped into 5 factor areas. The CDI is a widely used and accepted assessment for the severity of depressive symptoms with high reliability.

Patient Health Questionnaire (PHQ-9): adolescents

A depression-focussed screening tool such as the PHQ-9 is recommended by the US Preventive Sercives Task Force (USPSTF) for depression screening in adolescents.[65] The PHQ-9 is a psychological assessment for screening, diagnosing, and monitoring the severity of depression or dysthymic symptoms.[80] It is a brief self-report scale, and item 9 includes a screening question for suicidal ideation. Diagnostic validity has been established in primary care settings. Note that PHQ-9 contains a question on suicidality; given that a positive response necessitates urgent assessment, this is not an appropriate screening tool for remote screening when a clinician is not immediately available to monitor and act on positive responses (e.g., via patient portal in advance of well visits in primary care).[66]

Depression rating scales may also facilitate measurement of response to treatment over time ('measurement-based treatment').[66]

Screening for suicidal ideation

Although the USPSTF found insufficient evidence to recommend routine screening for suicide risk in children and adolescents in primary care, the American Academy of Pediatrics (AAP) recommends that paediatricians screen all youth aged 12 years and older for suicide risk at least annually.[65] [81] The AAP notes that screening at every visit may be indicated for higher risk populations, such as those presenting with psychiatric problems such as depression.[68]

The AAP notes that the accident and emergency department plays a key role in identifying children and youth at immediate risk for suicidality, regardless of whether they are at risk for depression. Use of a brief validated screening tool for suicidality, for example, the Ask Suicide Screening Questions (ASQ) (validated in children aged 10 years and over) or Columbia Suicide Severity Rating Scale for pediatrics (C-SSRC) (validated in children and adults aged 12 years and over) may be helpful in this setting.[82] [83] [84]

Screening for suicidal ideation in adolescents should typically take place in a confidential manner, without carers present, given that young people may be reluctant to report suicidal ideation in the company of carers. Use of a brief suicide safety assessment (BSSA) is recommended by the AAP for all patients screening positive for suicide risk, in order to further explore their personal risk and protective factors. Note that the BSSA is different from the initial screening tool, which simply identifies risk.[69]

It is imperative to ask about access to lethal means (firearms, medicines, illicit substances, knives, ropes) in the event of a positive screen for suicidal ideation, followed by risk-tailored counselling and mitigation.[68] [70] A positive screening result for suicidal ideation should be followed safety planning, an intervention that encompasses helping the patient identify their risk factors for suicidal ideation as well as a series of supports that they can draw on to reduce their risk of self-harm. Children and adolescents who are depressed with severe suicidality without being able to maintain safety, or with significant psychosis, require urgent referral to the accident and emergency department. See: Suicide risk mitigation .

Approach

The following treatment recommendations are based on published treatment guidelines.[66] [67][85] [86]

It is crucial to make an accurate diagnosis, based on a comprehensive assessment and review of the history, with input from multiple sources. The safety of the child and others, and the duration and severity of depression, need to be evaluated carefully to help determine the appropriate level of care and treatment modality. Ongoing assessments of safety, symptoms, and treatment response are important in limiting adverse events and in optimising and guiding the treatment approach.

Confidentiality should be discussed with the patient and his or her family, including the limits of confidentiality (e.g., the need to inform parents or legal authorities if there is an imminent risk of harm to the patient or to others [in keeping with clinicians' local legal frameworks]).[64]

Generalist versus specialist care

Depression in children and adolescents presents with a broad phenotype and psychosocial complexity. It is important for physicians to appreciate the scope of practice that is required to safely and effectively manage the care of a young person with depression. Subsequent sections about treatment will specifically emphasise which interventions should ideally or only be provided under specialist provider care, and the remainder of the text will apply to generalist care.

Generalists include general practitioners, paediatricians, and general adult psychiatrists with limited experience of children and youth. Specialists include accredited child and youth psychiatrists and general adult psychiatrists with extensive experience of children and youth.

Generalists manage mild to moderate severity with or without simple comorbidity, and their treatments are well supported by evidence. Specialists manage moderate to severe illness, often with complex comorbidity. Evidence for treatment may be lacking.

Phases of treatment

The treatment of depression can be divided into 3 phases.

- Acute: lasting for 6 to 12 weeks; the goal of this phase is to achieve remission (i.e., for the patient to become asymptomatic or to have minimal symptoms only).
- Continuation: immediately follows the acute phase, and lasts for 6 to 12 months (ideally 6 months for first episode and 12 months for recurrent episode); the goal of this phase is to prevent relapse. The same treatment regimen that was effective for acute treatment should be continued. Without continuing effective treatment, relapse rates are very high, as demonstrated in both psychotherapy and medication studies.[87] In the case of fluoxetine, even with continuation of treatment, many children and adolescents relapse. It has also been found that adding 6 months of continuation-phase cognitive behavioural therapy (CBT) after acute CBT significantly lowered relapse rates compared with historical controls (6% vs. 50%).[88]
- Maintenance: follows the continuation phase in some people; 1 to 2 years of the maintenance treatment may be recommended for young people at risk for recurrence (e.g., those with high genetic loading, chronic depression, multiple episodes, and severe episodes). One small paediatric depression maintenance study has been reported.[89] Although a larger study is needed, maintenance treatment is recommended by treatment guidelines.

Establishing a good therapeutic alliance with both the child and the parents, providing psychoeducation, and including family in the treatment decision-making process may improve adherence and promote positive outcomes throughout the treatment phases. As suicidal thoughts are a symptom of the disorder, and entail increased safety risk for the patient, suicidal thoughts should be monitored regularly during the assessment and treatment phases, and assessed at each clinical encounter.[68]

Urgent measures for children at risk of harm to themselves or others

Suicidal behaviours such as self-harm and suicide attempts are common in children and adolescents with depression. The most important aspect of care is for the clinician to be aware of the extent of these behaviours in the patient. At the initial consultation and follow-up appointments, the patient should be asked about self-harm; troubleshoot about the reasons for it that may be modifiable, and ensure that the patient has not made an interim suicide or self-harm attempt.

It is recommended that health care professionals screen adolescents for suicidal ideation without carers present, given that young people may be reluctant to report suicidal ideation in the company of carers. However, it is important to discuss both the importance of and the limitations of confidentiality with patients and their families before seeing the patient alone.[68] The limits of confidentiality include scenarios when breaching confidentiality is necessary to protect patient and/or public safety. This can be a challenging area and requires clinical judgment, as well as knowledge of local/state/national legal frameworks; external advice from an ethics or risk management consultant may be beneficial. It is important to note that recent or active suicidal ideation (including suicide attempts) must always be communicated to a responsible adult in order to protect the minor from harm, and to involve the carer in necessary treatment.[68] Ideally, and if at all possible, this should be done with the consent of the patient.

Children and adolescents experiencing suicidal ideation, particularly those who have suicidal ideation and a history of suicide attempts, require safety planning.[68] Safety planning is an intervention carried out in collaboration between the patient and a health care professional, for example, therapist or care manager, that encompasses helping the patient identify their risk factors for suicidal ideation as well as a series of supports that they can draw on to reduce their risk of self-harm.[68] Part of the safety plan involves helping the patient be aware of local crisis support services and ideally would involve carers in its development.

Children and adolescents who are depressed with severe suicidality and without being able to maintain safety, or with significant psychosis, require urgent referral to the emergency department. Hospitalisation may be necessary to:[90]

- Carry out an urgent mental healthcare assessment
- Ensure safety for the patient and/or for others
- Stabilise the patient.

See: Suicide risk mitigation .

Initial step in all patients: brief active monitoring

For mild or brief uncomplicated depression, a brief period of up to 6 weeks of active monitoring, with supportive care including psychoeducation for the child and parents, may be appropriate.[67][85] [86] [91] Mild depression often resolves with non-specific treatment. It may be necessary to cut the monitoring period short if symptoms are severe or worsen.

If the depression becomes severe, or suicidality or psychosis develops, immediate active treatment and higher levels of care (e.g., inpatient treatment) may be required.

A lifestyle assessment and recommendations for changes in diet and exercise may facilitate treatment and achieve better outcomes. There is growing evidence in support of the use of physical exercise to prevent and treat depressive disorders. Several controlled studies have demonstrated that exercise has an efficacy comparable with antidepressant therapy, and superior efficacy compared with placebo, in reducing depressive symptoms in adults.[92] One study indicated that regular exercise significantly reduced the risk of developing dysthymia in adults.[93] A meta-analysis of randomised controlled trials of exercise (4 trials, 159 participants) confirmed previous reviews by finding a medium-sized treatment effect (effect size -0.59, 95% CI -1.08 to -0.10) favouring exercise, but the investigators cautioned there was a high risk of bias in the included studies.[94] Another meta-analysis that included both randomised and non-randomised trials of exercise (10 trials, 431 participants) found a small- to medium-sized effect in reducing symptoms (effect size -0.49, 95% CI -0.71 to -0.24), but again the authors cautioned that the quality of included studies was low.[95]

Usually no further therapy is required, apart from the management of comorbid disorders and specific resistant individual symptoms, unless the depression increases in severity or symptoms persist.

Adjunctive treatment

Typically, adjunctive medications are instituted to manage symptoms associated with mild depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. One important issue is the duration of treatment. Because some depressive symptoms may take a long time to resolve, certain patients may need adjunctive medications early on during the acute treatment phase.

For psychotic depression or agitation, an atypical antipsychotic medication may be used concomitantly with an antidepressant. This would be necessary only if the antidepressant therapy was not controlling these symptoms adequately. For mild and low-risk psychotic symptoms or agitation an antidepressant may be sufficient, because the psychotic symptoms may resolve as depression improves.

Some of these drugs are considered off-label in some countries and are only to be prescribed by a specialist experienced in the treatment of paediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America and the UK.[66] [67][85]

Comorbid disorders

This is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Antidepressants may not sufficiently resolve insomnia. Behavioural interventions are the mainstay of treatment. In older children and adolescents, cognitive behavioural therapy for insomnia (CBT-I) may be considered, as in adults. Specific principles of behavioural interventions in this group include:

- Education on healthy sleep practices, e.g., a regular sleep-wake cycle, and guidance what constitutes a developmentally appropriate amount of sleep
- Avoidance of electronic devices with light-emitting screens at least one hour before bedtime
- Advice to use the bed for sleep only, and to get out of bed if unable to fall asleep
- Relaxation techniques

Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions alone. Note that prescribing is considered off-label in most parts of the world, the evidence base in children is very limited, and there is wide variation in prescribing geographically. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

Mild depression

For mild depression that does not respond to active monitoring, a course of specific evidence-based psychotherapy, such as CBT (including digital CBT) or interpersonal psychotherapy (IPT), if available and appropriate, may be used.[66] [67][97] [98] CBT has also been shown to have long-term effects on prevention of depression onset.[99] In the UK, the National Institute for Health and Care Excellence guidelines recommend the consideration of attachment-based family therapy for children with depression continuing after a period of watchful waiting.[67]

Moderate or severe depression

Specific psychotherapies or selective serotonin-reuptake inhibitors (SSRIs), or a combination, may be used for children and young people with depression of moderate or greater severity as first-line treatment.[100]

US guidelines recommend any of the following approaches for young people with depression of moderate or greater severity:[64] [66][85]

- Specific psychotherapies (e.g., CBT, IPT, dialectical behavioural therapy)
- SSRI medication
- A combination of specific psychotherapy and SSRI therapy
- Switching drugs or combination pharmacotherapy if there has been inadequate response.

UK guidelines recommend an initial trial of psychotherapy for all young people with depression of moderate or greater severity. Antidepressants are recommended only in combination with psychotherapy and generally after a trial of psychotherapy; however, combined therapy with fluoxetine and psychotherapy may be considered for initial treatment of moderate to severe depression in young people aged 12 to 18 years.[67] The distinction between these national recommendations is that US guidelines include SSRI monotherapy as first-line treatment for moderate to severe depression.

Studies to support this recommendation include one randomised controlled trial of moderately to severely depressed adolescents in which CBT plus SSRI was no more effective than SSRI alone.[101] There was no increase in disinhibition, irritability, and violence from baseline with either treatment.[101] Time to response is faster with fluoxetine than with psychological therapy, but suicide-related behaviours are also more common.[102]

The importance of concurrent or first-line psychotherapy is supported by long-term results and safety outcomes. Combination therapy may decrease suicidal ideation more than medication alone.[103] In a

meta-analysis of combined medication and psychotherapy versus medication alone, there was greater improvement in global functioning with combination treatment, but no difference was reported between the groups on depressive symptom reduction.[104]

In summary, considering both short- and long-term evidence of relative benefits of monotherapy and combination therapy for moderate to severe depression, it is reasonable to consider monotherapy with an SSRI or specific psychotherapy as the initial approach, and, if there is an inadequate response, treatment could be augmented and continued with combined SSRI and psychotherapy. The SSRI fluoxetine is typically the treatment of first choice based on meta-analysis data, although note that treatment effects may vary between individuals, and so individualised risk:benefit analysis is required when selecting an SSRI.[105] [106] [107] [108] In particular, fluoxetine is preferable over other SSRIs when time to remission is a high priority, and can be complemented by regular risk assessment in regards to suicidality by any professional. Psychological therapy is the treatment of first choice when maintaining safety is a high priority. This is salient when a young person with major depressive disorder has prominent suicide ideation, or has engaged in self-harm.

SSRIs: general considerations

SSRIs are the drug of choice, if a drug is required, and are often used after non-pharmacological steps have failed. A meta-analysis including 36 trials (6778 participants) found that SSRIs seem to be more beneficial than placebo for treating children and adolescents with depression, but that the effect size was small. The results suggest that, for children and adolescents with depression, the placebo effect plays a significant role in the efficacy of SSRIs.[109] The US Food and Drug Administration (FDA) issued a black box warning on suicidality associated with paediatric use of antidepressants in 2004.[110]

When discussing the use of an SSRI for treatment of depression, it is important to set realistic expectations for the child and carer. Not all children with depression will respond to an SSRI. Response, if positive, is subtle and gradual and requires physician monitoring. Not all depressive symptoms will respond to an SSRI; thus, it is important to consider adjunct interventions, mostly environmental, for those symptoms (e.g., sleep and pleasurable activity scheduling, appropriate nutrition and exercise, and classroom accommodations).

In addition, when starting medication, ensure the carer appreciates the importance of monitoring the administration and safe-keeping of medication. Many children struggle with compliance and sometimes misuse or attempt to overdose on medications. Deciding on safe-keeping of the medication in the home or the use of small-dose packaging is essential in this regard.

Fluoxetine

- The benefits of fluoxetine are supported by a strong body of meta-analysis data in both children and adolescents.[105] [106][107] [108]
- Doses may be increased incrementally after initial starting regimen if there is not sufficient improvement (<50% of reduction in depression severity) of depressive symptoms.[111] Adolescents may be more likely to need an increase to a higher dose than children.[112]
- Fluoxetine may have greater and more rapid efficacy in premenstrual dysphoric disorder.[113]
- Fluoxetine has the longest half-life of the recommended SSRIs (4-6 days in adults) and is a potent inhibitor of cytochrome P450 enzyme 2D6 and 2C19. When concomitant medications that are metabolised by these enzymes are used, a reduced dose may be considered.

- There is evidence to suggest that fluoxetine during the first trimester of pregnancy may be associated with a slightly increased risk of congenital heart malformations in the baby. In consideration of this finding, the physician should also take into account the established conferred risk to the fetus and newborn when the adolescent mother is depressed.[114]

Escitalopram

- May be used as a first-choice antidepressant for adolescents, but not children. One trial that included children and adolescents demonstrated positive results for escitalopram over placebo in the adolescent subgroup.[115]
- It is the active S-enantiomer of citalopram, with double the potency of citalopram. It has a half-life of 27 to 32 hours. Similar to citalopram, it is a weak 2D6 inhibitor with minimal drug-to-drug interactions.

Sertraline

- Has been found to be more effective than placebo only when the results of two trials were pooled.[116]
- It has a 26-hour half-life and is a moderate P450 enzyme inhibitor, although at high doses it is a potent inhibitor of 2D6. At high doses, drug-to-drug interactions need to be considered. Stronger evidence for efficacy in anxiety and obsessive-compulsive disorder.

Citalopram

- Has only one positive trial.[117]
- It has minimal effect on the P450 enzyme system, thus limited drug-to-drug interactions. Use caution at higher doses due to risk of prolongation of the QT interval.

Due to a lack of efficacy and being poorly tolerated in children, paroxetine is not recommended for use in children.[66] [118] [119] [120]

There are no paediatric depression trials for fluvoxamine.

Adverse effects and safety of SSRIs

Overall, most of the SSRIs and non-SSRIs (considered for use in later steps) are well tolerated by children and adolescents, and adverse effects are mild and short-lived. However, potential adverse effects and precautions need to be discussed thoroughly with the child and parents, to ensure safety and improve adherence. Children and adolescents treated for depression with SSRIs (and serotonin–noradrenaline reuptake inhibitors [SNRIs]) appear to experience a greater number of adverse effects (including severe adverse effects) than those treated with placebo, indicating a need for a careful and individualised approach to prescribing that considers the relationship between anticipated clinical benefit and possible side effects.[109] The FDA issued a black box warning on suicidality associated with paediatric use of antidepressants in 2004.[110] Common adverse effects of SSRIs include:

- Headaches
- Nausea
- Diarrhoea
- Abdominal pain
- Insomnia
- Sedation

- Tremors
- Increased bleeding time.

Sexual adverse effects related to SSRIs occur frequently in adults and adolescents (up to 40% of patients), but these adverse effects are not always discussed at patient review.

Most of these effects may be mitigated by simple strategies, such as:

- Initiating medication at a low dose
- Titrating slowly
- Taking medication with food, to avoid nausea or gastric discomfort
- Taking sedating medications at bedtime and alerting medication in the morning.

Uncommon but more concerning adverse events include:

- Activation
- Induction of manic/hypomanic symptoms
- Suicidal thoughts and behaviours.

A careful review of family history, first-degree relatives' response to medication, previous medication history, and concurrent use of other medications for potential drug-to-drug interactions may better prepare the patient, family, and clinician to avoid negative consequences. These considerations may also help the clinician make the initial medication choice.

Suicidal thoughts are part of the presentation of depression, and may occur prior to or during treatment. Although there is insufficient evidence to support suggestions that antidepressants could cause suicidal ideation and behaviour, both the FDA analysis and a re-analysis of all the controlled trials of antidepressant therapy have indicated an increased association of suicidal ideation but not suicide attempt with antidepressant treatment versus placebo. The risk is relatively small, comprising only a 1% to 2% increased risk of suicidal ideation with antidepressant use (3% to 4%) compared with placebo (2%).[121] [122] Eleven times more youth who are treated with an antidepressant will respond to the medication than will develop suicidal behaviour.[121] It is recommended that children and adolescents should be monitored closely during the early weeks of initiating antidepressant treatment and during dose adjustments. Rating scales may be used to assess and monitor adverse effects and adverse events during depression treatment, such as:

- Safety Monitoring Uniform Report Form[123]
- Toronto Side Effects Scale[124]
- Liverpool University Neuroleptic Side Effects Scale[125]
- Mental Health Therapeutic Outcomes Tool.[126]

Children need to be monitored closely with a more frequent follow-up schedule when initiating a new treatment, or during dose change, as adverse effects and adverse events are more likely to occur during those periods. A minimum of 1 to 2 visits (either face to face or virtual) every 4 weeks during the initial months of antidepressant treatment is required.

Moderate or severe depression: inadequate improvement with first SSRI

If, after 8 or more weeks of treatment with an SSRI at an adequate dose (either as a monotherapy or combined with specific psychotherapy), there is no response (no change in depression severity or functioning impairment), or only partial response (less than a significant reduction of depression severity

or improvement of functioning), switching to another SSRI is recommended. Choices of a second SSRI include fluoxetine, sertraline, citalopram, and escitalopram (escitalopram is for adolescents only), depending on which was used initially. If evidence-based psychotherapy was not used initially, it should be actively instituted at this point in treatment.[127]

Moderate or severe depression: management of inadequate response to second SSRI by switching to a non-SSRI (specialist care)

If there is an inadequate response after the second SSRI, then the medication can be switched to a non-SSRI, or the SSRI could be augmented. It should be noted that current evidence to support switching to a non-SSRI or augmenting does not exist for children and adolescents. As such, these agents should only be commenced by specialists who are experts in managing depression in childhood.

Before initiating this step, a careful reassessment is important to verify the diagnosis and to rule out other contributing factors, such as unrecognised or newly emergent comorbid illness (e.g., substance use disorder), inadequacy of psychosocial intervention, unresolved stress, or a new trauma.

Choices for switching include:

- Venlafaxine
- Mirtazapine
- Bupropion.

SNRIs seem to be more beneficial than placebo for treating children and adolescents with depression, although the effect size is small. One meta-analysis found that children and adolescents treated with SNRIs reported a greater incidence of adverse effects than those treated with placebo, including serious adverse effects such as suicidality, emphasising the need for a careful and individualised harm-benefit analysis prior to considering treatment.[109]

Venlafaxine

An SNRI. To assess the efficacy of this treatment, three controlled studies have been conducted, and all were negative. However, when the data from two studies was pooled together, the adolescent subgroup showed that venlafaxine was superior compared with placebo in reducing depression.[128] [129] Venlafaxine is not recommended as a first-line choice. However, the only controlled trial for treatment-resistant depression indicated that venlafaxine was effective in treating depression in adolescents who did not respond to one SSRI.[127] In the FDA assessment, compared with other antidepressants, venlafaxine did have significantly more suicide-related adverse events than placebo.[122] A retrospective cohort study of 36,842 patients aged 6 to 18 years showed no evidence that risk of suicide attempts differed for SSRI and SNRI antidepressants.[130] Extended-release formula is recommended, which still has a relatively short half-life of 10.3 hours. UK guidelines recommend that venlafaxine should not be used for the treatment of depression in children and young people.[67]

Mirtazapine

A serotonin receptor 2 (5-HT2) antagonist, with a half-life of 20 to 40 hours. The only two multicentre paediatric mirtazapine trials were negative, possibly due to the high placebo response in the two studies.[131] The drug does not inhibit any P450 enzymes. At lower dose, mirtazapine has a strong antihistamine effect, and may also cause sedation and weight gain.

Bupropion

A potent 2D6 inhibitor with a half-life of 21 hours for the sustained-release formulation. There have been no controlled trials for bupropion, although it is frequently prescribed.[110]

Moderate or severe depression: management of inadequate response to second SSRI by augmentation strategies (specialist care)

An alternative approach to switching to a non-SSRI medication is to use augmentation strategies, especially if there is a partial response to the second SSRI. Psychotherapy (e.g., CBT or IPT) or medication may be used to augment.

In adults, lithium, triiodothyronine, atypical antipsychotic medications, and bupropion have been studied most frequently, with some indications of efficacy.[132] [133] [134] [135] [136] [137] [138] Atypical antipsychotics and bupropion have been used more frequently in the paediatric population as augmenting agents compared with other agents. However, paediatric controlled studies have not been done. These agents should only be commenced by specialists who are experts in managing depression in childhood. The only study of paediatric treatment-resistant depression found that adolescents who had more than nine CBT sessions in addition to treatment with a second SSRI or venlafaxine were more likely to have a positive response than adolescents who received fewer CBT sessions.[139]

Bupropion is one of the more frequently used augmenting agents, although no paediatric trials have been conducted on it. Sustained-release bupropion may be used to augment.

Atypical antipsychotics have been used clinically to augment antidepressant effect. Quetiapine, aripiprazole, and ziprasidone are used more frequently in clinical settings, because risperidone and olanzapine may cause significant weight gain and metabolic effects. No controlled trials have been conducted in depressed children, although a chart review of 10 cases indicated the efficacy of adding quetiapine to treat depressed adolescents who have not responded to an adequate trial of an SSRI. For all other atypical antipsychotics except ziprasidone, weight, lipid profile, and fasting glucose need to be monitored.

Lamotrigine has been studied in the management of unipolar depression and bipolar depression, though studies are limited. In one study that included chart reviews of 42 adolescent patients with treatment-resistant depression, 22 showed improvement with lamotrigine.[140]

Lithium has been studied as an augmenting agent most frequently in adults, with more than 10 controlled trials. In most of the studies, lithium was used as an augmenting agent for tricyclic antidepressants (TCAs). Only two open paediatric trials also used lithium to augment a TCA.[141] [142] Blood levels need to be monitored to avoid toxicity. Thyroid and renal function also need to be monitored regularly.

Levothyroxine has been studied, but its efficacy is inconclusive according to adult depression data. Neither controlled nor open trials have been done in the paediatric population. Thyroid-stimulating hormone levels need to be monitored to avoid negative biofeedback.

Novel alternative approaches for children with treatment-resistant depression (specialist care)

If response remains poor, despite all of the possible treatments outlined up to this phase, novel and alternative treatments may be considered. These should only be commenced by specialists who are experts in managing depression in childhood. They include:

- Other antidepressants (e.g., TCAs and monoamine oxidase inhibitors [MAOIs])
- Biological treatments (e.g., light therapy and electroconvulsive therapy [ECT]).

Other antidepressants, such as TCAs or MAOIs, may be used for children and adolescents who have not responded to SSRIs or non-SSRIs. TCAs have not proved to be effective in treating paediatric depression, and tend to produce more adverse events.[143] UK guidelines recommend that TCAs should not be used for the treatment of depression in children and young people.[67] Because of the adverse effects and the difficulty of managing diet in children and adolescents, MAOIs have not been recommended for use in paediatric depression. However, the patch form of a selective MAOI, selegiline, may bypass the concern and become an alternative treatment for young people with depression resistant to other treatment. A study comparing the selegiline patch and placebo in adolescents with major depressive disorder demonstrated safety of the active medication, although response rates were similar for both groups (58.6% vs. 59.3%).[144]

Biological treatments include light therapy and ECT. Light therapy is recommended for seasonal affective disorder (SAD), and its efficacy has been demonstrated in a few case series and one controlled study in young people with SAD.[145] A recent review and meta-analysis indicates that light therapy may be effective for non-seasonal depression in adults.[146]

Case reports on the efficacy of ECT in paediatric depression have appeared for more than 60 years.[147] However, there have not been any controlled trials conducted in the paediatric population. Series reports indicate that the best response is in youth with catatonia, psychosis, and bipolar depression. There is a negative perception regarding ECT in some countries, including in several US states, where the use of ECT in children and adolescents has been banned. This, and the fact that generally medication and psychotherapy are readily available, has led to infrequent use of ECT as a treatment modality, even in children and young people with treatment-resistant depression.

Complementary and alternative medicine treatment (CAM)

Although complementary and alternative medicine is used frequently around the world for treating paediatric depression, including in the US, there is extremely limited empirical evidence for its efficacy.[148] UK guidelines states that St. John's wort should not be prescribed for the treatment of depression in children and young people, due to insufficient evidence of efficacy and known drug interactions.[67] US guidelines have not discussed the use of natural remedies in the management of paediatric depression.

Among the natural remedies, the most frequently used and studied remedies for depression include:

- St. John's wort
- Omega-3 fatty acids
- S-adenosyl methionine (SAMe).

St. John's wort is the most frequently used herbal remedy for depression. It is the number one antidepressant prescribed for children in Germany.[149] There are many adult-controlled studies that

indicate inconsistent efficacy in treating adult depression.[150] [151] No controlled studies have been conducted in children with depression. Several open-label studies indicate that St. John's wort is well tolerated by children, and that it is effective in treating depression in children.[152] [153] [154] However, it is not recommended to treat moderate to severe cases of depression, due to unclear efficacy. St. John's wort has also been associated with longer coagulation time; in addition, it increases metabolism of contraceptives and can result in unwanted pregnancy. Caution is necessary with concurrent use of other medications, due to potential drug-to-drug interactions. This is a particular concern with concurrent use of other antidepressants, because of the risk of serotonergic syndrome.

Omega-3 fatty acids are suggested to be beneficial in many health problems. A combination of eicosapentaenoic acid and docosahexaenoic acid from fish oil, rather than omega-3 fatty acids from plants, is effective. Results from adult depression studies indicate benefit in reducing depression.[155] Only one small controlled study of depressed children has been done. This demonstrated that 70% of children who received 1000 mg daily dose of omega-3 fish oil, versus 0% of children who received placebo, had a reduction in their depression severity.[156] Fish oil is well tolerated in general, but high doses are not recommended due to inhibition of platelet aggregation and concern for potential bleeding. Fish oil may also interact with anticoagulants, so it is not recommended for use concurrently with those drugs. There is a concern about contamination of fish oil from heavy metals and pesticides. Algae omega-3 may be a purer alternative source of omega-3 fatty acids compared with fish oil.

SAMe is important in the synthesis of neurotransmitters, such as serotonin, noradrenaline (norepinephrine), and dopamine. Adult depression trials of SAMe indicated superior efficacy to placebo and comparable efficacy to TCAs.[157] SAMe may also be effective as an augmenting agent.[158] No paediatric depression studies are available, except for case reports that indicate efficacy in treating depression in children and adolescents.[159] Interactions of SAMe with other medications appear to be infrequent.[151]

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

Initial		(summary)
at risk of suicidality		
	1st	**risk-tailored suicide mitigation**

Acute (summary)		
mild		
	1st	active monitoring + supportive care
	adjunct	management of associated symptoms and comorbid disorders
	2nd	specific psychotherapy + supportive care
	adjunct	management of associated symptoms and comorbid disorders
moderate or severe		
	1st	selective serotonin-reuptake inhibitor (SSRI) + supportive care
	adjunct	management of associated symptoms and comorbid disorders
	1st	psychotherapy + supportive care
	adjunct	management of associated symptoms and comorbid disorders
	1st	selective serotonin-reuptake inhibitor (SSRI) + psychotherapy + supportive care
	adjunct	management of associated symptoms and comorbid disorders
	2nd	switch to a different selective serotonin-reuptake inhibitor (SSRI) + psychotherapy + supportive care
	adjunct	management of associated symptoms and comorbid disorders
	3rd	switch to a non-selective serotonin-reuptake inhibitor + psychotherapy + supportive care
	adjunct	management of associated symptoms and comorbid disorders
	4th	augmentation of second selective serotonin-reuptake inhibitor (SSRI) with psychotherapy or with another medication + supportive care
	adjunct	management of associated symptoms and comorbid disorders
	5th	novel alternative approaches + supportive care
	adjunct	management of associated symptoms and comorbid disorders

Ongoing		(summary)
following stabilisation of acute symptoms		
	1st	**continuation therapy for 6 to 12 months**
	adjunct	**maintenance therapy for 1 to 2 years**

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

Initial

at risk of suicidality

1st **risk-tailored suicide mitigation**

» Children and adolescents experiencing suicidal ideation, particularly those who have suicidal ideation and a history of suicide attempts, require safety planning.[68] Safety planning is an intervention carried out in collaboration between the patient and a health care professional, for example, therapist or care manager, that encompasses helping the patient identify their risk factors for suicidal ideation as well as a series of supports that they can draw on to reduce their risk of self-harm.[68] Part of the safety plan involves helping the patient be aware of local crisis support services and ideally would involve carers in its development.

» It is imperative to ask about access to lethal means (firearms, medicines, illicit substances, knives, ropes) when suicidal ideation or a plan is disclosed, followed by risk-tailored counselling and mitigation.[68] [70]

» When considering confidentiality and its limitations, it is important to note that recent or active suicidal ideation (including suicide attempts) must always be communicated to a responsible adult in order to protect the patient from harm, and to involve the carer in necessary treatment.[68] Ideally, and if at all possible, this should be done with the consent of the patient. Confidentiality and its limitations, for example, when a breach of confidentiality is required in order to protect the patient and/or public safety, can be a challenging area and requires clinical judgment, as well as knowledge of local/state/national legal frameworks; external advice from an ethics or risk management consultant may be beneficial.

» Children and adolescents who are depressed with severe suicidality without being able to maintain safety, or with significant psychosis, require urgent referral to the emergency department.

» Hospitalisation may be necessary to carry out an urgent mental healthcare assessment; ensure safety for the patient and/or for others; and stabilise the patient.[90]

Initial

» See: Suicide risk mitigation .

Acute

mild

1st **active monitoring + supportive care**

» For mild or brief uncomplicated depression, a brief period of up to 6 weeks of active monitoring, with supportive care including psychoeducation for the child and parents, may be appropriate.[67][85] [86] [91] Mild depression often resolves with non-specific treatment.

» A lifestyle assessment, and recommendations for changes in diet and exercise, may facilitate treatment and achieve better outcomes. Several controlled studies have demonstrated that exercise has an efficacy comparable with antidepressant therapy, and superior efficacy compared with placebo, in reducing depressive symptoms in adults, but paediatric evidence is still limited.[92]

» A meta-analysis of randomised controlled trials of exercise (4 trials, 159 participants) confirmed previous reviews by finding a medium-sized treatment effect (effect size -0.59, 95% CI -1.08 to -0.10) favouring exercise, but the investigators cautioned there was a high risk of bias in the included studies.[94] Another meta-analysis that included both randomised and non-randomised trials of exercise (10 trials, 431 participants) found a small- to medium-sized effect in reducing symptoms (effect size -0.49, 95% CI -0.71 to -0.24), but again the authors cautioned that the quality of included studies was low.[95]

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, immediate treatment and high levels of care (e.g., inpatient treatment) may be required.

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then,

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sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with mild depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g., agitation) may take a long time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

2nd **specific psychotherapy + supportive care**

» If the response to active monitoring is inadequate, a course of specific evidence-based psychotherapy, such as cognitive behavioural therapy (CBT; including digital CBT) or interpersonal psychotherapy, if available and appropriate, may be used.[67][97] [98]

» In the UK, the National Institute for Health and Care Excellence guidelines recommend the consideration of attachment-based family therapy for children with depression continuing after a period of watchful waiting.[67]

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, immediate treatment and high levels of care (e.g., inpatient treatment) may be required.

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety

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disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with mild depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g., agitation) may take a longer time to resolve, so some patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

moderate or severe

1st **selective serotonin-reuptake inhibitor (SSRI) + supportive care**

Primary options

» fluoxetine: children <8 years of age: consult specialist for guidance on dose; children ≥8 years of age: 10 mg orally once daily initially, increase according to response, maximum 60 mg/day

OR

» escitalopram: children <12 years of age: consult specialist for guidance on dose; children ≥12 years of age: 10 mg orally once

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daily initially, increase according to response, maximum 20 mg/day

OR

» sertraline: children <10 years of age: consult specialist for guidance on dose; children ≥10 years of age: 25 mg orally once daily initially, increase according to response, maximum 200 mg/day

OR

» citalopram: children <7 years of age: consult specialist for guidance on dose; children ≥7 years of age: 10 mg orally once daily initially, increase according to response, maximum 40 mg/day (20 mg/day in poor metabolisers of CYP2C19)

» For moderate or severe depression, antidepressant treatment with an SSRI may be initiated.

» The SSRI fluoxetine is the treatment of first choice based on meta-analysis data, although note that treatment effects may vary between individuals, and so individualised risk:benefit analysis is required when selecting an SSRI.[105] [106] [107] [108] In particular, fluoxetine it is preferable over other SSRIs when time to remission is a high priority, and can be complemented by regular risk assessment in regards to suicidality by any professional. Psychological therapy is the treatment of first choice when maintaining safety is a high priority. This is salient when a young person with major depressive disorder has prominent suicide ideation, or has engaged in self-harm.

» The results of one meta-analysis suggest that SSRIs are more beneficial than placebo for treating children and adolescents with depression, although the effect size is small. The placebo effect appears to play a significant role in the efficacy of SSRIs. Children and adolescents treated with SSRIs reported a greater incidence of adverse effects than those treated with placebo, including serious adverse effects such as suicidality, emphasising the need for a careful and individualised harm-benefit analysis prior to treatment.[109]

» When discussing the use of an SSRI for treatment of depression, it is important to set realistic expectations for the child and carer. Not all children with depression will respond to

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an SSRI. Response, if positive, is subtle and gradual and requires physician monitoring. Not all depressive symptoms will respond to an SSRI; thus, it is important to consider adjunct interventions, mostly environmental, for those symptoms (e.g., sleep and pleasurable activity scheduling, appropriate nutrition and exercise, and classroom accommodations). In addition, when starting medication, ensure the carer appreciates the importance of monitoring the administration and safe-keeping of medication.

» A minimum of 1 to 2 visits every 4 weeks during the initial months of antidepressant treatment is required.

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, high levels of care (e.g., inpatient treatment) may be required.

» Doses and age cut-offs stated here may be off-label in some countries; consult your local guidance. These drugs are only to be prescribed by a specialist experienced in the treatment of paediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America and the UK.[67] [85] [91]

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g.,

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agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

1st **psychotherapy + supportive care**

» Specific psychotherapies may also be used for children and young people with depression of moderate or greater severity as first-line treatment.[100]

» UK guidelines recommend an initial trial of psychotherapy for all young people with depression of moderate or greater severity. US guidelines recommend either specific psychotherapies, medication, or their combination for young people with depression of moderate or greater severity.[85]

» Specific psychotherapies can include cognitive behavioural therapy, interpersonal psychotherapy, and dialectical behavioural therapy.[67]

» The importance of concurrent or first-line psychotherapy is supported by long-term results and safety outcomes. Results from one study indicate that combination therapy may decrease suicidal ideation more than medication alone.[103]

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, high levels of care (e.g., inpatient treatment) may be required.

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid

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disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g., agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

1st **selective serotonin-reuptake inhibitor (SSRI) + psychotherapy + supportive care**

Primary options

» fluoxetine: children <8 years of age: consult specialist for guidance on dose; children ≥8 years of age: 10 mg orally once daily initially, increase according to response, maximum 60 mg/day

OR

» escitalopram: children <12 years of age: consult specialist for guidance on dose; children ≥12 years of age: 10 mg orally once daily initially, increase according to response, maximum 20 mg/day

OR

» sertraline: children <10 years of age: consult specialist for guidance on dose;

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children ≥10 years of age: 25 mg orally once daily initially, increase according to response, maximum 200 mg/day

OR

» citalopram: children <7 years of age: consult specialist for guidance on dose; children ≥7 years of age: 10 mg orally once daily initially, increase according to response, maximum 40 mg/day (20 mg/day in poor metabolisers of CYP2C19)

» US guidelines recommend either specific psychotherapies, medication, or their combination for young people with depression of moderate or greater severity.[85] UK guidelines recommend an initial trial of psychotherapy for all young people with depression of moderate or greater severity. Antidepressants are recommended only in combination with psychotherapy and generally after a trial of psychotherapy; however, combined therapy with fluoxetine and psychotherapy may be considered for initial treatment of moderate to severe depression in young people aged 12 to 18 years.[67]

» The SSRI fluoxetine is the treatment of first choice based on meta-analysis data, although note that treatment effects may vary between individuals, and so individualised risk:benefit analysis is required when selecting an SSRI.[105] [106] [107] [108] In particular, fluoxetine is preferable over other SSRIs when time to remission is a high priority, and can be complemented by regular risk assessment in regards to suicidality by any professional. Psychological therapy is the treatment of first choice when maintaining safety is a high priority. This is salient when a young person with major depressive disorder has prominent suicide ideation, or has engaged in self-harm.

» The importance of concurrent or first-line psychotherapy is supported by long-term results and safety outcomes. Combination therapy may decrease suicidal ideation more than medication alone.[103] In a meta-analysis of combined medication and psychotherapy versus medication alone, there was greater improvement in global functioning with combination treatment, but no difference was reported between the groups on depressive symptom reduction.[104]

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» The results of one meta-analysis suggest that SSRIs are more beneficial than placebo for treating children and adolescents with depression, although the effect size is small. The placebo effect appears to play a significant role in the efficacy of SSRIs. Children and adolescents treated with SSRIs reported a greater incidence of adverse effects than those treated with placebo, including serious adverse effects such as suicidality, emphasising the need for a careful and individualised harm-benefit analysis prior to treatment.[109]

» When discussing the use of an SSRI for treatment of depression, it is important to set realistic expectations for the child and carer. Not all children with depression will respond to an SSRI. Response, if positive, is subtle and gradual and requires physician monitoring. Not all depressive symptoms will respond to an SSRI; thus, it is important to consider adjunct interventions, mostly environmental, for those symptoms (e.g., sleep and pleasurable activity scheduling, appropriate nutrition and exercise, and classroom accommodations). In addition, when starting medication, ensure the carer appreciates the importance of monitoring the administration and safe-keeping of medication.

» A minimum of 1 to 2 visits every 4 weeks during the initial months of antidepressant treatment is required.

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, high levels of care (e.g., inpatient treatment) may be required.

» Doses and age cut-offs stated here may be off-label in some countries; consult your local guidance. These drugs are only to be prescribed by a specialist experienced in the treatment of paediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America and the UK.[66][67][85]

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not

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recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g., agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

2nd **switch to a different selective serotonin-reuptake inhibitor (SSRI) + psychotherapy + supportive care**

Primary options

» fluoxetine: children <8 years of age: consult specialist for guidance on dose; children ≥8 years of age: 10 mg orally once daily initially, increase according to response, maximum 60 mg/day

OR

» escitalopram: children <12 years of age: consult specialist for guidance on dose; children ≥12 years of age: 10 mg orally once daily initially, increase according to response, maximum 20 mg/day

OR

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» sertraline: children <10 years of age: consult specialist for guidance on dose; children ≥10 years of age: 25 mg orally once daily initially, increase according to response, maximum 200 mg/day

OR

» citalopram: children <7 years of age: consult specialist for guidance on dose; children ≥7 years of age: 10 mg orally once daily initially, increase according to response, maximum 40 mg/day (20 mg/day in poor metabolisers of CYP2C19)

» If, after 8 weeks of treatment with an SSRI at an adequate dose, there is no response (no change in depression severity or functioning impairment), or only partial response (less than a significant reduction of depression severity or improvement of functioning), switching to another SSRI is recommended, as well as the addition of cognitive behavioural therapy.

» The results of one meta-analysis suggest that SSRIs are more beneficial than placebo for treating children and adolescents with depression, although the effect size is small. The placebo effect appears to play a significant role in the efficacy of SSRIs. Children and adolescents treated with SSRIs reported a greater incidence of adverse effects than those treated with placebo, including serious adverse effects such as suicidality, emphasising the need for a careful and individualised cost-benefit analysis prior to treatment.[109]

» When discussing the use of an SSRI for treatment of depression, it is important to set realistic expectations for the child and carer. Not all children with depression will respond to an SSRI. Response, if positive, is subtle and gradual and requires physician monitoring. Not all depressive symptoms will respond to an SSRI; thus, it is important to consider adjunct interventions, mostly environmental, for those symptoms (e.g., sleep and pleasurable activity scheduling, appropriate nutrition and exercise, and classroom accommodations). In addition, when starting medication, ensure the carer appreciates the importance of monitoring the administration and safe-keeping of medication.

» A minimum of 1 to 2 visits every 4 weeks during the initial months of antidepressant treatment is required.

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» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, high levels of care (e.g., inpatient treatment) may be required.

» Doses and age cut-offs stated here may be off-label in some countries; consult your local guidance. These drugs are only to be prescribed by a specialist experienced in the treatment of paediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America and the UK.[66][67][85]

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g., agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[67] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for

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insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

3rd **switch to a non-selective serotonin-reuptake inhibitor + psychotherapy + supportive care**

Primary options

» mirtazapine: consult specialist for guidance on dose

OR

» bupropion: consult specialist for guidance on dose

» At this stage it is important to reassess the patient in order to verify the diagnosis and to rule out other contributing factors, such as unrecognised or newly emergent comorbid illness (e.g., substance use disorder), inadequacy of psychosocial intervention, unresolved stress, or a new trauma.

» Switching to an antidepressant that is not an SSRI is recommended if a second SSRI produces minimal to no response. Choices for switching include mirtazapine, bupropion, and venlafaxine. These agents should only be commenced by specialists who are experts in managing depression in childhood. UK guidelines recommend that venlafaxine should not be used for the treatment of depression in children and young people.[67]

» The results of one meta-analysis suggest that serotonin–noradrenaline reuptake inhibitors (SNRIs) are more beneficial than placebo for treating children and adolescents with depression, although the effect size is small. The placebo effect appears to play a significant role in the efficacy of SNRIs. Children and adolescents treated with SNRIs reported a greater incidence of adverse effects than those treated with placebo, including serious adverse effects such as suicidality, emphasising the need for a careful and individualised cost-benefit analysis prior to considering treatment.[109]

» Venlafaxine did have significantly more suicide-related adverse events than placebo in one assessment.[122]

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, high levels of care (e.g., inpatient treatment) may be required.

Acute

» These drugs are only to be prescribed by a specialist experienced in the treatment of paediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America and the UK.[66] [67] [85]

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g., agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

4th **augmentation of second selective serotonin-reuptake inhibitor (SSRI) with psychotherapy or with another medication + supportive care**

Acute

Primary options

» fluoxetine: children <8 years of age: consult specialist for guidance on dose; children ≥8 years of age: 10 mg orally once daily initially, increase according to response, maximum 60 mg/day
-or-
» escitalopram: children <12 years of age: consult specialist for guidance on dose; children ≥12 years of age: 10 mg orally once daily initially, increase according to response, maximum 20 mg/day
-or-
» sertraline: children <10 years of age: consult specialist for guidance on dose; children ≥10 years of age: 25 mg orally once daily initially, increase according to response, maximum 200 mg/day
-or-
» citalopram: children <7 years of age: consult specialist for guidance on dose; children ≥7 years of age: 10 mg orally once daily initially, increase according to response, maximum 40 mg/day (20 mg/day in poor metabolisers of CYP2C19)

--AND--

» bupropion: consult specialist for guidance on dose
-or-
» quetiapine: consult specialist for guidance on dose
-or-
» aripiprazole: consult specialist for guidance on dose
-or-
» ziprasidone: consult specialist for guidance on dose
-or-
» risperidone: consult specialist for guidance on dose
-or-
» olanzapine: consult specialist for guidance on dose
-or-
» lamotrigine: consult specialist for guidance on dose
-or-
» lithium: consult specialist for guidance on dose

» At this stage it is important to reassess the patient in order to verify the diagnosis and to rule out other contributing factors, such as unrecognised or newly emergent comorbid illness (e.g., substance use disorder),

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inadequacy of psychosocial intervention, unresolved stress, or a new trauma.

» As an alternative to switching to an antidepressant that is not a SSRI, it is possible to augment the existing SSRI with either psychotherapy or another medication.

» Atypical antipsychotics and bupropion have been used more frequently in the paediatric population as augmenting agents, compared with other agents. However, paediatric controlled studies have not been done. These agents should only be commenced by specialists who are experts in managing depression in childhood.

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, high levels of care (e.g., inpatient treatment) may be required.

» Doses and age cut-offs stated here may be off-label in some countries; consult your local guidance. These drugs are only to be prescribed by a specialist experienced in the treatment of paediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America and the UK.[66][67][85]

adjunct **management of associated symptoms and comorbid disorders**

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of

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all severities. Some depressive symptoms (e.g., agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

5th **novel alternative approaches + supportive care**

» If response remains poor despite all of the possible treatments outlined up to this phase, novel alternative treatments may be considered. These should only be commenced by specialists who are experts in managing depression in childhood.

» Other antidepressants, such as tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs), may be used for children and adolescents who have not responded to SSRIs or non-SSRIs. TCAs have not been shown to be effective in treating paediatric depression and tend to produce more adverse events.[143] UK guidelines recommend that TCAs should not be used for the treatment of depression in children and young people.[67] Because of the adverse effects and difficulty of managing diet in children and adolescents, MAOIs have not been recommended for use in paediatric depression.

» Biological treatments include light therapy and electroconvulsive therapy (ECT). There have not been any controlled trials of ECT conducted in the paediatric population. In several US states, ECT in children and adolescents has been banned.

» If there is an acute progression of symptoms and depression becomes severe, or if suicidality or psychosis develops, high levels of care (e.g., inpatient treatment) may be required.

adjunct **management of associated symptoms and comorbid disorders**

Acute

Treatment recommended for SOME patients in selected patient group

» Comorbid disorders: this is an important consideration at all steps of treatment. Anxiety disorders and ADHD are common comorbid disorders. Psychotherapy for an anxiety disorder may be started concomitantly with antidepressant treatment. However, it is not recommended to start both an antidepressant and another medication to treat a comorbid disorder simultaneously. The primary illness, or the disorder causing the most impairment of function, needs to be treated first. Then, sequentially, a second and third treatment to target comorbid disorders may be initiated if required (e.g., a stimulant may be started sequentially with an antidepressant).

» Associated symptoms: typically, adjunctive medications are instituted to manage symptoms associated with depression (e.g., agitation) and are discontinued when the target symptom resolves. Adjunctive therapy may be required in any of the treatment steps for depression of all severities. Some depressive symptoms (e.g., agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase.

» Insomnia is a frequent symptom of depression and also a frequent residual symptom.[96] Using an evidence-based psychosocial intervention such as cognitive behavioural therapy for insomnia (CBT-I) may be helpful to resolve insomnia early during acute treatment. Occasionally, medication in combination with behavioural therapy may be considered for children and adolescents whose insomnia is unresponsive to behavioural interventions. Clinicians should consult local service models, but typically consideration of medication for insomnia in children requires referral to a paediatric sleep clinic or other specialist setting.

Ongoing

following stabilisation of acute symptoms

1st **continuation therapy for 6 to 12 months**

» Once remission is achieved, whether it is after the first medication or psychotherapy treatment or after multiple treatment trials, treatment is continued for 6 to 12 months to avoid relapse, at the same dose used for acute treatment. Recommendation is 6 months for first episode, 12 months for recurrent episode.

adjunct **maintenance therapy for 1 to 2 years**

Treatment recommended for SOME patients in selected patient group

» Following the period of continuation therapy, 1 to 2 years of maintenance treatment may be needed for children who are at risk of having recurrent depression (multiple episodes, chronic depression, comorbid disorders).

» One small paediatric depression maintenance study has been reported.[89] Although a larger study is needed, maintenance treatment is recommended by treatment guidelines.

Emerging

Transcranial magnetic stimulation (TMS)

There is emerging evidence that repetitive TMS (rTMS) maybe safe and effective for treating depression in adolescents.[160] [161]

Vagus nerve stimulation (VNS)

There is evidence to support the use of VNS in adult treatment-resistant depression.[162] [163] [164] However, there have been no trials for paediatric depression. Because of the invasive nature of the procedure and potential adverse effects, it is not recommended for use in treating paediatric depression.

Transdermal selegiline

Because of the adverse effects and the difficulty of managing diet in children and adolescents, monoamine oxidase inhibitors have not been recommended for use in paediatric depression. However, the transdermal patch formulation of selegiline may bypass the concern and become an alternative treatment for young people with depression resistant to other treatment. One study comparing the selegiline patch and placebo in adolescents with major depression disorder demonstrated safety of the active medication, although response rates were similar for both groups (58.6% versus 59.3%).[144]

Ketamine

Ketamine is a glutamate receptor N-methyl-D-aspartate antagonist, and has been investigated for its antidepressant effect. Glutamate is thought to play an important role in cellular plasticity and resilience.[165] Ketamine has been found to induce a rapid antidepressant response (within hours) in treatment-resistant depression in adults. A study of 18 treatment-resistant depressed adults found a rapid and sustained (1-2 week) antidepressant effect.[166] No paediatric studies have been conducted, but the results from adult studies are promising. The long-term safety and efficacy of ketamine in adults (and by extension in children) remains unclear.[167] A systematic review of 60 articles looking at side effects in adults with depression treated with single and repeated doses of ketamine found that acute side effects were common, and were more likely to occur in patients given intravenous ketamine. The majority of side effects resolved shortly after drug administration. They included psychiatric (most commonly anxiety), psychotomimetic, cardiovascular, and neurological effects. The most common reported effects were headache, dizziness, dissociation, raised blood pressure, and blurred vision. The authors note that insufficient data were available regarding the risks associated with repeated dosing, and that more data are needed on the potential cumulative and long-term risks in patients with depression requiring repeated doses of ketamine over a long period of time. Repeated use of ketamine in other patient groups has been linked to urological and liver toxicity, cognitive deficits, and dependency. Ketamine dependency is a known disorder.[168] The experimental nature of ketamine dosing, the potential for increased suicide risk, and unknown long-term effects should be considered, particularly in the population for which this medication is often indicated: vulnerable patients at risk for death from suicide.

New drug development

Medications targeting different systems (other than serotonin or noradrenaline [norepinephrine]) have been investigated. Studies have found that agomelatine (a melatonin receptor agonist and serotonin 2c receptor antagonist) surpassed placebo and fluoxetine in reducing depression severity and improving sleep, and sertraline in regulating the circadian rest-activity, regulating the sleep-wake cycle, reducing depressive and anxiety symptoms, and preventing relapse in depressed adults.[169] [170] [171] [172]

Primary prevention

Stressful life events, history of trauma, chronic illness, and parental depression play important roles in paediatric depression. Efforts to reduce stress and trauma, and to treat parental depression, could potentially decrease the likelihood of depressive disorders in children. School-, community-, or internet-based cognitive behavioural prevention programmes may be a useful preventive measure in at-risk adolescents.[59] [60]

[61] Recent attention has been given to utilising technology in preventing depression. In one New Zealand study of high school students, those who received daily messages over 9 weeks reported that the messages helped them to be more positive and reduce negative thoughts compared with students who did not receive messages.[62] Additional research on the role of technology in prevention and treatment is needed.

Treating other psychiatric illnesses, such as ADHD and anxiety disorders, could also potentially reduce the incidence of depressive disorder.

Secondary prevention

Safety needs to be assessed prior to and throughout the treatment of depression, as suicidal thoughts and behaviours may present during all stages of depression. Frequent follow-up visits during the early phase of treatment and during dose change is important, to monitor adverse effects and to assess safety and treatment response. Risky behaviour, and substance use, need to be routinely assessed. The treatment also should aim at preventing relapse, as the relapse rate in childhood depression is high.

Patient discussions

Education of the parents and child about depression is important. It is important to explain to the patient and carers that:

- Depression is common in children and teenagers.
- Depression may present as feelings of anger, moodiness, and increased anxiety rather than predominantly as sadness.
- A paediatrician, family doctor, child psychiatrist, or a counsellor may all be asked to treat a patient with depression
- There are different types of treatment, including psychotherapy, medication, or both
- There are different choices of medications, and they often take several weeks before there is any apparent improvement
- Most medications used to treat depression are well tolerated by most people
- Frequent visits to the doctor after starting a medication are important to make sure that the medication is safe, is helping, and is not causing adverse effects
- Treatment changes may be required
- It is important that the patient actively participates in the treatment and works with the doctor to find the best treatment for them (although it is normal for children and adolescents have periods of treatment non-compliance)
- Carer involvement is critical to depression treatment success.

FOLLOW UP

Monitoring

Monitoring

After treatment is initiated, weekly to bi-weekly follow-up visits are needed to monitor adverse effects and symptom change and response. Ongoing assessment of functioning in several key domains is required (home, school, and peer settings), as well as assessments of suicidality.[85] If a child makes good progress and the treatment is an appropriate choice for the child, the visit frequency may be reduced to once every 4 to 6 weeks during the continuation phase of treatment. Despite guidelines recommending regular follow-up care, the majority of youth being treated with antidepressants do not receive adequate follow-up care.[176] Monitoring during the continuation phase of treatment is also important, as the relapse rate is high. Compliance becomes a bigger issue during the continuation phase of treatment. Having a good relationship with patients and their families may improve adherence.

Part of the monitoring should also include asking about engagement in therapy. Most children being monitored for depression should have access to a therapist or counsellor. It is important to determine whether the child is regularly attending, and whether they find any benefit. If not, encourage them or their carers to speak to the therapist. This is particularly important if the child is not progressing or is getting worse.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
treatment-induced mania, agitation, or disinhibition	**short term**	**low**
Although rare, activation or a manic or hypomanic episode can be induced by antidepressants. A careful review of family history and symptoms is important to rule out a bipolar illness or low tolerance of antidepressants. In addition, careful monitoring and ongoing assessment of symptom change and response are important to detect such occurrence early, and to take appropriate steps to avoid negative outcomes.		
suicidal behaviour	**variable**	**medium**
Suicidal ideation occurs more frequently than suicidal behaviour and suicide attempts in young people with depressive disorder. However, depression is the most frequent psychiatric illness among suicide completers.[174] Suicidal thoughts and behaviours may occur prior to or during treatment. There is a slight increased risk of suicidality (1% to 2%) associated with antidepressant use (3% to 4%) compared with placebo (2%).[121] [122] The US Food and Drug Administration issued a black box warning on suicidality associated with paediatric use of antidepressants in 2004.[110] Ongoing assessment of safety is important, and children need to be monitored closely, especially during the early weeks of initiating antidepressant treatment and during dose change. It is important to alert carers to this possibility and to co-develop a safety plan with the child.[175] Minors should not manage their own medication at home under most circumstances.		
aggression	**variable**	**low**
Children and adolescents with depressive disorder may be irritable and angry. Childhood depression is also highly comorbid with disruptive behaviour disorders. Occasionally, antidepressants may increase agitation. Careful assessment of irritability, anger, and aggressive behaviour, prior to and during treatment, is important to prevent serious consequences. Care level and medications may need to be adjusted, and other disorders may need to be considered.		
substance use disorder	**variable**	**low**
Depression increases the risk of substance use disorder.[66] They are less common in younger children but increases in older adolescents. If a child is not responding to treatment, a concurrent use or misuse of a substance needs to be ruled out. Questions about substance use need to be asked routinely and, if regular substance use is identified, motivational interviewing about perceived impact of substance use and desire to reduce its use is indicated. When there are concerns about atypical presentations or intoxications, periodic drug screening may help clarify drug exposures. Drug screening is not required for depression treatment in children and adolescents without known substance use problems.		

Prognosis

Childhood depression, like depression in adulthood, is a chronic and recurrent illness that causes significant morbidity and mortality. A major depressive episode may remit spontaneously (even without treatment) within 1 to 2 years, but may last up to 9 months in clinical samples.[91] About 50% to 60% of young people respond to the first psychotherapy or medication treatment that was tried. An additional 40% and 50% of young people who do not respond to at least one medication trial respond when switching to a new antidepressant, or switching to a new antidepressant plus psychotherapy.[127] However, once improved, the relapse or recurrence rate is high. Following recovery from a depressive episode, it is estimated that about 40% of young people have a relapse of the index episode, or a recurrence (new episode) of a major depressive episode within 2 years after remission, and up to 70% at 5 years after remission. Depressed young people spend up to 30% of their lives in a depressive episode, which causes significant impairment in academic and social functioning and increases the risk for suicide and substance use disorders.[66] One UK-based cohort study (n=3884) found that the presence of severe affective symptoms in adolescents (both anxiety and depressive symptoms) was associated with an increased risk of premature mortality over a 53-year follow-up period. (In the study, affective symptoms were rated by teachers using a rating scale that pre-dated the introduction of diagnostic criteria.)[173] As such, it is critically important for clinicians to identify the presence of depression, and associated comorbidities, and to begin evidence-based treatment as early as possible.

GUIDELINES

Diagnostic guidelines

United Kingdom

Depression in children and young people: identification and management (https://www.nice.org.uk/guidance/ng134)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

North America

Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders (https://www.aacap.org/AACAP/Practice/Clinical%20Practice%20Guidelines/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx)

Published by: American Academy of Child and Adolescent Psychiatry **Last published:** 2022

Screening for depression in children and adolescents: U.S. Preventive Services Task Force recommendation statement (https://jamanetwork.com/journals/jama/fullarticle/2797145)

Published by: US Preventive Services Task Force **Last published:** 2022

Guidelines for adolescent depression in primary care (GLAD-PC): Part I. Practice preparation, identification, assessment, and initial management (https://pediatrics.aappublications.org/content/141/3/e20174081)

Published by: American Academy of Pediatrics **Last published:** 2018

Treatment guidelines

United Kingdom

Depression in children and young people: identification and management (https://www.nice.org.uk/guidance/ng134)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

North America

Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders (https://www.aacap.org/AACAP/Practice/Clinical%20Practice%20Guidelines/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx)

Published by: American Academy of Child and Adolescent Psychiatry **Last published:** 2022

Guidelines for adolescent depression in primary care (GLAD-PC): Part I. Practice preparation, identification, assessment, and initial management (https://pediatrics.aappublications.org/content/141/3/e20174081)

Published by: American Academy of Pediatrics **Last published:** 2018

Adolescent depression in primary care (GLAD-PC): Part II. Treatment and ongoing management (https://pediatrics.aappublications.org/content/141/3/e20174082.long)

Published by: American Academy of Pediatrics **Last published:** 2018

Online resources

1. Duke University: Mood and Feelings Questionnaire (https://devepi.duhs.duke.edu/measures/the-mood-and-feelings-questionnaire-mfq) *(external link)*

Key articles

- Zuckerbrot RA, Cheung A, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC): Part I. Practice preparation, identification, assessment, and initial management. Pediatrics. 2018 Mar;141(3):e20174081. Full text (https://publications.aap.org/pediatrics/article/141/3/e20174081/37626/Guidelines-for-Adolescent-Depression-in-Primary) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29483200?tool=bestpractice.bmj.com)

- Walter HJ, Abright AR, Bukstein OG, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. J Am Acad Child Adolesc Psychiatry. 21Oct 2022 [Epub ahead of print]. Full text (https://www.jaacap.org/article/S0890-8567(22)01852-4/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36273673?tool=bestpractice.bmj.com)

- National Institute for Health and Care Excellence. Depression in children and young people: identification and management. Jun 2019 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng134)

- Hua LL, Lee J, Rahmandar MH, et al. Suicide and suicide risk in adolescents. Pediatrics. 2024 Jan 1;153(1):e2023064800. Full text (https://publications.aap.org/pediatrics/article/153/1/e2023064800/196189/Suicide-and-Suicide-Risk-in-Adolescents) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/38073403?tool=bestpractice.bmj.com)

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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