# Table of Contents

## Summary
- 3

## Basics
- Definition 4
- Epidemiology 4
- Etiology 4
- Pathophysiology 4
- Classification 5

## Prevention
- Primary prevention 8
- Screening 8
- Secondary prevention 9

## Diagnosis
- Case history 10
- Step-by-step diagnostic approach 10
- Risk factors 14
- History & examination factors 16
- Diagnostic tests 18
- Differential diagnosis 19
- Diagnostic criteria 23

## Treatment
- Step-by-step treatment approach 27
- Treatment details overview 36
- Treatment options 38
- Emerging 59

## Follow up
- Recommendations 60
- Complications 60
- Prognosis 61

## Guidelines
- Diagnostic guidelines 62
- Treatment guidelines 63

## Online resources
- 65

## Evidence scores
- 66

## References
- 67

## Disclaimer
- 80
<table>
<thead>
<tr>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>◊ Characterized 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.</td>
</tr>
<tr>
<td>◊ One of the most common pediatric psychiatric disorders, especially among girls during adolescence.</td>
</tr>
<tr>
<td>◊ 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.</td>
</tr>
<tr>
<td>◊ 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.</td>
</tr>
<tr>
<td>◊ There is an increased risk for substance abuse, suicide attempts, and completed suicide. Suicidality needs to be assessed at each healthcare encounter.</td>
</tr>
<tr>
<td>◊ Following recovery, relapse or recurrence rate is high in the absence of continuation treatment.</td>
</tr>
</tbody>
</table>
**Definition**

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) categorizes depressive disorders in children into the following categories: major depressive disorder (MDD), persistent depressive disorder (dysthymia), 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 (dysthymia). MDD in children is a more severe form of depressive disorder, and is characterized 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 characterized 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. A meta-analysis of 26 epidemiologic studies (over 60,000 observations on children born between 1965 and 1996) found an estimated prevalence rate of depressive disorder among children under 13 years to be 2.8%, and among children between 13 and 18 years to be 5.6%.[2] Among these epidemiologic studies, 1 study surveyed 1420 children ages 9 to 13 years from North Carolina and found a 3-month prevalence of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV depressive disorders (major depressive disorder and dysthymia) to be 0.9 in children and 3.1 in adolescents.[3] Rates are similar in boys and girls, but depression becomes twice as common in adolescent girls compared with adolescent boys, which is consistent with sex ratios in adult depression.[4] The cumulative prevalence, or lifetime prevalence rate, of major depression by the end of adolescence is much higher than in earlier childhood (up to 25%).[5] Although there have been reports of increased secular trends of the prevalence of depression in clinical samples, there is no evidence that the rates of depressive disorder among children have increased in the general population for the past 30 years.[2] Depressive disorders may be higher in indigenous children,[6] and in children with chronic medical illness.[7]

**Etiology**

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.[8] [9] [10]

**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 pediatric population, and some of the adult findings have not been demonstrated in childhood depression. For example, cortisol hypersecretion, a consistent finding among depressed adults, was not replicated in depressed children.[11] However, there is evidence indicating the dysregulation of the central serotonergic systems in childhood depression. Prepubertal depressed children were found to have attenuated cortisol, but increased prolactin secretion responding to L-5-hydroxytryptophan challenge.[12]
Depression in children

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.[13] [14]

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.[15] [16] [17] [18] The results in outpatients have been mixed.[19] [20] [21]

The disruption in the motivation-and-reward neurologic pathway has also been indicated in pediatric depression.[22] There is evidence of the involvement of the glutamatergic system in the pathophysiology of depressive disorders.[23] Increased morning cortisol in youth at risk for depression predicts onset of depression.[24] 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, behavioral inhibition, and in the manifestation of depressive symptoms.[25] [26] [27] [28]

Classification


Categorizes depressive disorders in children into the following categories: major depressive disorder (MDD), persistent depressive disorder (dysthymia), 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 (dysthymia).

MDD

• Similar to adults, characterized by at least 5 depressive symptoms, occurring over the same 2-week period, although children and adolescents may have irritability instead of depression as 1 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.

Persistent depressive disorder (dysthymia)

• Includes DSM-IV-defined chronic MDD and dysthymic disorder.
• A more chronic form of depressive disorder than MDD.
• Characterized 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 and 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.
DMDD

- A new category of depressive disorders for children 6 to 18 years of age, with age of onset before 10 years of age.
- Characterized by severe and persistent irritability or angry mood nearly every day, and severe and recurrent temper outbursts at least 3 times a week.
- Symptoms are inconsistent with developmental level, present in at least 2 out of 3 settings (i.e., home, school, and with peers) and are severe in at least one setting.
- Symptoms have occurred for at least 12 months and during this time the child must not have gone 3 or more consecutive months without symptoms.
- There have never been symptoms lasting for more than 1 day that meet the criteria for a manic or hypomanic episode except for duration.
- Symptoms do not occur during an MDD episode and are not better accounted for by another mental disorder, and are not due to a substance/medication or other medical condition.

Premenstrual dysphoric disorder

- An independent category of depressive disorders in DSM-5.
- Characterized by at least 5 mood symptoms that have been present a week before the onset of the majority of menstrual cycles in the preceding year. Symptoms become minimal or absent within a few days after the onset of menses.
- At least one symptom is one of the following symptoms: marked affective lability (mood swing), marked irritability or anger or interpersonal conflict, marked depression, and marked anxiety or tension.
- At least one symptom is one of the following symptoms: anhedonia, poor concentration, fatigue, change in appetite, insomnia or hypersomnia, sense of feeling out of control/overwhelmed, and physical symptoms (e.g., aches and pains, sensation of bloating).
- Symptoms cause significant distress or interference with functioning and are not part of, or an exacerbation of, another disorder.
- Symptoms are not due to a substance/medication or another medical condition.

Substance/medication-induced depressive disorder

- Marked, persistent, and function-impairing depressed mood or anhedonia caused by a substance or medication.
- Symptoms developed during or soon after exposure to a substance or medication known to cause the types of depressive symptoms.
- Symptoms are not better accounted for by an independent, nonsubstance/medication-induced depressive disorder, and do not occur exclusively during the course of a delirium.

Depressive disorder due to another medical condition

- Marked, persistent, and function-impairing depressed mood or anhedonia caused by another medical condition.
- Symptoms are not better accounted for by another mental disorder, and do not occur exclusively during the course of a delirium.

Other specified depressive disorder and unspecified depressive disorder

- Formerly known (in DSM-IV) as depressive disorder not otherwise specified.
- Symptoms do not meet the criteria for any of the other depressive disorder categories.
• Characterized by fewer depressive symptoms, or shorter duration, than the other types of depressive disorders.
• Examples of the other specified depressive disorder include recurrent brief depressive disorder and short-duration depressive episode.
• The unspecified depressive disorder does not specify the reason for not meeting criteria for other depressive disorder categories.
Primary prevention

Stressful life events, history of trauma, chronic illness, and parental depression play important roles in pediatric 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 behavioral prevention programs may be a useful preventive measure in at-risk adolescents.[53] [54] [55] Recent attention has been given to utilizing 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.[56] 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.

Screening

Children and adolescents with risk factors seen at primary care settings need to be screened for depressive disorder.[59] [60] 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.

Annual universal screening in a primary care setting is recommended for all children ages 12 years and older, even in the absence of specific risk factors, according to US-based guidance.[57] Children who come to a psychiatric facility always need to be screened for depression because depression is highly comorbid with other psychiatric disorders.

Screening should be completed by direct clinician interview, in addition to screening instruments.[57]

Reynolds adolescent/child depression scales (RADS/RCDS)

The RADS/RCDS[61] [62] is a child- and parent-report depression instrument, with useful psychometric properties. It is an effective screening tool, but probably not a good instrument for monitoring treatment outcomes.[63] 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.[64] It is a good screening tool and can be used in both clinical and research settings.[65] It can be accessed online for clinical or research use. [Duke University: Mood and Feelings Questionnaire] A short version of the MFQ (MFQ-SF) was found to be sensitive in screening for major depressive disorder among youths ages 11 to 17 in a primary care setting.[66]

Beck depression inventory (BDI)

The BDI is a widely used adolescent self-rated depression scale with good psychometric properties.[67] [63] 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. 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

The PHQ-9 is a psychological assessment for screening, diagnosing, and monitoring the severity of depression or dysthymic symptoms. 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.

Secondary prevention

Safety needs to be assessed prior to and throughout the treatment of depression, as suicidal thoughts and behaviors 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 behavior, and substance use and abuse, need to be routinely assessed. The treatment also should aim at preventing relapse, as the relapse rate in childhood depression is high.
Case history

Case history #1

A 15-year-old girl, in the 10th grade 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 2 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 behavior over the past 4 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 in the 3rd grade, attending a local public school. His parents say that he has been mean 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 hospitalized 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.

Step-by-step diagnostic approach

Adolescent and preadolescent 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, counselors).

Initial concerns about symptoms and signs may be brought to the attention of the physician by the parents, other caregivers, or by the child or adolescent themselves. Alternatively, the diagnosis may be made following screening. Children and adolescents with risk factors for depressive illness, who are seen at primary care settings, need to be screened for depressive disorder. Annual universal screening in a primary care setting is recommended for all children ages 12 years and older, even in the absence of specific risk factors, according to US-based guidance.[57] Children who come to a psychiatric facility always need to be screened for depression, because depression is highly comorbid with other psychiatric disorders.
There is no specific test for childhood depression. Hypothyroidism, anemia, 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 complete blood count (CBC) with differential and thyroid function test 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 the parents should be interviewed separately. Screening should be completed by direct clinician interview, in addition to screening instruments.[57]

For adolescents in particular, interviewing them first may improve cooperation. 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 preadolescent 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 exclude differential diagnoses and formulate the treatment plan:

- Developmental history
- Medical history
- Presence of comorbid psychiatric disorders, substance use or abuse
- 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 a chronic medical condition, postpartum status, neighborhood and social instability, and the use of immunosuppressive medications.

**Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5): criteria for major depressive episode**

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 or suicidal ideation
- 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 episode.

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 judgment of the severity of the depressive disorder based on global functional impairment ratings, and the severity and number of symptoms present. 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 (DSM-5): criteria for persistent depressive disorder (previously known as dysthymia in DSM-IV)

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
- Fatigue
- Decreased 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.

**Presenting symptoms**

Both the child and the parents should be asked about specific depressive symptoms, based on the DSM-5 diagnostic criteria. Common symptoms include sad and/or irritable mood, decreased concentration and school performance, diminished enjoyment of activities, fatigue, 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. Although not a DSM-5 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 and 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.

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:[57]

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

A safety assessment, including for suicidality, should be completed by the clinician.[57]

**Impairment**

An assessment of functional impairment resulting from the current depressive symptoms needs to be included. Depressive symptoms need to cause significant impairment in 1 or more areas of functioning (e.g., school, home, social settings) to meet DSM-5 criteria for MDD or persistent depressive disorder (dysthymia). Information regarding the severity of depressive symptoms and functioning impairment will guide the treatment approach.
Depression frequently co-occurs with substance abuse during adolescence. In addition, some substances are known to cause depressive symptoms. According to the DSM-5 diagnostic criteria, a diagnosis of MDD 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.

**Examination**

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

- Infectious mononucleosis
- Vitamin deficiencies
- Anemia
- Substance abuse
- 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 exam and subsequent workup. 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).

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 judgment will help determine an appropriate level of care and treatment approach. Psychomotor agitation or retardation may be noted.

**Investigations**

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

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

**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.
- 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.
- Children with depressed parents are 2-4 times more likely to have depression.
Depression in children

Diagnosis

- Both maternal and paternal depression have been linked to depression and other psychiatric disorders in children.[32] [33] [34] This impacts children through both genetic and environmental effects, and is associated with more marital conflict, poor parenting, and decreased support.[35] [36]

other parental psychopathology

- In addition to parental depression, high rates of other parental psychopathology (e.g., alcohol abuse, substance disorders, suicidal behaviors, anxiety disorders) have been found in children and adolescents with depression.[37] [38]

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

- Childhood depressive disorder is highly comorbid with other psychiatric disorders.
- Comorbid anxiety disorders occur in 30% to 80% of children with depression, and comorbid disruptive disorders occur in 10% to 80%. These conditions are most frequently comorbid with depressive disorders, and frequently precede depression.[39]

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.[40]

female sex

- Increases susceptibility to depression, particularly during adolescence.
- By adolescence, the prevalence rate of depression in females is almost twice that of depression in males.[4]

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.[41] LGBTQ youth also have higher rates of abuse that account for some of this disparity.[42] [43]

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.[44] [45]

postpartum status

- About 10% to 20% of women giving birth develop postpartum depression.[46] [47] Up to 48% of adolescent mothers in the US have been found to have depressive symptoms (surveyed at a mean of 17 months postpartum).[48] [49]

neighborhood and social instability

- Neighborhood instability, violence, and poor resources provided by the school and neighborhood have been associated with the development of childhood depression and other psychopathologies.[37] [50]

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

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

substance use/abuse

- Depression frequently co-occurs with substance abuse during adolescence. There is evidence that substance abuse may increase the risk of developing depressive disorders, and some substances are known to cause depressive symptoms.[51] [52]

History & examination factors

Key diagnostic factors

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 Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnostic criteria for major depressive disorder (MDD).
- Irritable mood could be as common as sad mood.
- To meet DSM-5 MDD episode criteria, the mood must be present most of the day, almost every day, for at least 2 weeks, and coexist 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.

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 diagnostic criteria for major depressive disorder.

significant functional impairment (common)

- Depressive symptoms need to cause significant impairment in 1 or more areas of functioning (e.g., school, home, social settings) to meet DSM-5 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-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 program, 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-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-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-listed depressive symptoms for major depressive disorder and persistent depressive disorder (dysthymia).

feelings of worthlessness or excessive guilt (common)

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

psychomotor agitation or retardation (common)

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

somatic complaints (common)

- Although it is not a DSM-5 diagnostic criterion for major depressive disorder, excessive somatic complaints may be common in younger depressed children.

social withdrawal or change of friends (common)

- A common sign of a depressed child.

recurrent thoughts of death or suicidal ideation (uncommon)

- One of the DSM-5-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 abuse during adolescence.
- In addition, some substances are known to cause depressive symptoms.[51] [52] According to the DSM-5 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.
## Diagnosis

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>clinical diagnosis</strong></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Adolescent and preadolescent 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, counselors).*</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
</tbody>
</table>

### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>serum thyroid-stimulating hormone (TSH) and free thyroxine (T4)</strong></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Baseline assessment to exclude thyroid dysfunction. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Primary hypothyroidism: elevated TSH; free T4 may be low. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Hyperthyroidism: suppressed TSH; elevated free T4. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>complete blood count with differential</strong></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Baseline assessment to exclude anemia or other disorders. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Infectious mononucleosis: may show anemia, reticulocytosis, lymphocytosis, atypical lymphocytes. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Iron deficiency: microcytic, hypochromic anemia; low reticulocyte count. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Hypothyroidism: occasionally mild anemia; macrocytosis. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Vitamin B12 deficiency: elevated mean corpuscular volume, low hematocrit. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>urine drug screen</strong></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Baseline assessment test. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>urine pregnancy test</strong></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* Screen for pregnancy in females should also be completed. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>serum B12 and folate</strong></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* 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. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>vitamin D level</strong></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>* 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. *</td>
<td><img src="image.png" alt="Image" /></td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Bipolar disorder   | • Clinical examination using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 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 behavior 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.                                                                                                                                                                                                                                           | No differentiating test. |
| Anxiety disorder   | • Clinical examination using the DSM-5 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 disorders will improve outcome.                                                                                                                                                                                                                                                                                                                                                     | No differentiating test. |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>• Clinical examination using the DSM-5 criteria establishes differentiating symptoms and signs. Mood changes due to ADHD can be either due to a side effect of stimulants, or demoralization as a result of difficulties in school, with family, or with peers.</td>
<td>• No differentiating test.</td>
</tr>
<tr>
<td></td>
<td>• ADHD is diagnosed when full diagnostic criteria are met prior to age 7 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.</td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td>• Clinical examination using the DSM-5 criteria helps to establish differentiating symptoms and signs.</td>
<td>• Urine drug screen confirms concomitant use of substance.</td>
</tr>
<tr>
<td></td>
<td>• Substance abuse may precede depressive symptoms or occur as a consequence of depression.</td>
<td></td>
</tr>
<tr>
<td>Adjustment disorder with depressed mood</td>
<td>• A stressor always precedes the depressive symptoms. In addition, the depressive symptoms should not meet full DSM-5 criteria for major depressive disorder.</td>
<td>• No differentiating test.</td>
</tr>
<tr>
<td>Bereavement</td>
<td>• A recent loss of a loved one always precedes the depressive symptoms.</td>
<td>• No differentiating test.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
</tbody>
</table>
| 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-experiencing of the trauma, avoidance behavior, and increased anxiety or arousal. | • No differentiating test.            |
| Posttraumatic 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 behavior, and increased anxiety or arousal. | • No differentiating test.            |
| Oppositional defiant disorder  | • Clinical examination using the DSM-5 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.  
                                  • Behavioral problems are more chronic, and present without concurrent mood symptoms. | • No differentiating test.            |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Anorexia nervosa   | • Clinical examination using the DSM-5 criteria helps to establish differentiating signs and symptoms. Difficult to assess depressive status unless 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 criteria helps to establish differentiating symptoms and signs.  
• Additional symptoms, such as body image distortions and overeating, occur without mood symptoms.  
• However, eating disorders and depression can be comorbid. | • No differentiating test                                                                  |
| Thyroid dysfunction | • Hypothyroidism may be associated with weight gain and constipation. On examination there may be dry, coarse skin, goiter, 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 exam there may be goiter, tremor, 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 T3 are elevated. |
<p>| Anemia             | • May be associated with a history of poor nutrition, pallor, and prominent fatigue.            | • Complete blood count reveals low hemoglobin.                                          |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious mononucleosis</strong></td>
<td>• History of initial symptoms of fever, fatigue, malaise, pharyngitis, and cervical or generalized lymphadenopathy.</td>
<td>• Positive agglutination test (e.g., monospot) showing heterophile antibodies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Serologic test demonstrating Epstein-Barr virus-specific antibodies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Complete blood count with differential may demonstrate lymphocytosis, atypical lymphocytosis, anemia, and reticulocytosis.</td>
</tr>
<tr>
<td><strong>Vitamin deficiency</strong></td>
<td>• May be associated with a history of poor nutrition, pallor, and prominent fatigue.</td>
<td>• Complete blood count may reveal anemia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood levels of vitamins may be low. However, tests would only usually be performed if vitamin deficiency were considered a likely cause of symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Further specific tests of vitamin deficiency may be used to confirm deficiency.</td>
</tr>
<tr>
<td><strong>Temporal lobe epilepsy</strong></td>
<td>• History of recurrent and chronic focal seizures.</td>
<td>• Electroencephalogram reveals spikes or sharp waves in the temporal lobe area. This would only usually be performed if temporal lobe epilepsy were considered a likely cause of symptoms.</td>
</tr>
</tbody>
</table>

**Diagnostic criteria**

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

Categorizes depressive disorders in children into the following categories: major depressive disorder (MDD), persistent depressive disorder (dysthymia), 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 (dysthymia).

**DSM-5: criteria for major depressive episode**[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:
Depression in children

Diagnosis

- 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 or suicidal ideation
- 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 episode.

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 judgment of the severity of the depressive disorder based on global functional impairment ratings, and the severity and number of symptoms present. 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: criteria for persistent depressive disorder (dysthymia)**[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:
Depression in children

Diagnosis

• Sad or irritable mood
• Increased or decreased appetite
• Insomnia or hypersomnia
• Fatigue
• Decreased 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.

DSM-5: criteria for DMDD[1]

• A new category of depressive disorders for children 6 to 18 years of age, with age of onset before 10 years of age.
• Characterized by severe and persistent irritability or angry mood nearly every day, and severe and recurrent temper outbursts at least 3 times a week.
• Symptoms are inconsistent with developmental level, present in at least 2 out of 3 settings (i.e., home, school, and with peers) and are severe in at least one setting.
• Symptoms have occurred for at least 12 months and during this time the child must not have gone 3 or more consecutive months without symptoms.
• There have never been symptoms lasting for more than 1 day that meet the criteria for a manic or hypomanic episode except for duration.
• Symptoms do not occur during an MDD episode and are not better accounted for by another mental disorder, and are not due to a substance/medication or other medical condition.

DSM-5: criteria for premenstrual dysphoric disorder[1]

• An independent category of depressive disorders in DSM-5.
• Characterized by at least 5 mood symptoms that have been present a week before the onset of the majority of menstrual cycles in the preceding year. Symptoms become minimal or absent within a few days after the onset of menses.
• At least one symptom is one of the following symptoms: marked affective lability (mood swing), marked irritability or anger or interpersonal conflict, marked depression, and marked anxiety or tension.
• At least one symptom is one of the following symptoms: anhedonia, poor concentration, fatigue, change in appetite, insomnia or hypersomnia, sense of feeling out of control/overwhelmed, and physical symptoms (e.g., aches and pains, sensation of bloating).
• Symptoms cause significant distress or interference with functioning and are not part of, or an exacerbation of, another disorder.
• Symptoms are not due to a substance/medication or another medical condition.
**DSM-5: criteria for substance/medication-induced depressive disorder[1]**

- Marked, persistent, and function-impairing depressed mood or anhedonia caused by a substance or medication.
- Symptoms developed during or soon after exposure to a substance or medication known to cause the types of depressive symptoms.
- Symptoms are not better accounted for by an independent, nonsubstance/medication-induced depressive disorder, and do not occur exclusively during the course of a delirium.

**DSM-5: criteria for depressive disorder due to another medical condition[1]**

- Marked, persistent, and function-impairing depressed mood or anhedonia caused by another medical condition.
- Symptoms are not better accounted for by another mental disorder, and do not occur exclusively during the course of a delirium.

**DSM-5: criteria for other specified depressive disorder and unspecified depressive disorder[1]**

- Formerly known (in DSM-IV) as depressive disorder not otherwise specified.
- Symptoms do not meet the criteria for any of the other depressive disorder categories.
- Characterized by fewer depressive symptoms, or shorter duration, than the other types of depressive disorders.
- Examples of the other specified depressive disorder include recurrent brief depressive disorder and short-duration depressive episode.
- The unspecified depressive disorder does not specify the reason for not meeting criteria for other depressive disorder categories.
Step-by-step treatment approach

The following treatment recommendations are based on published treatment guidelines, including the Practice Parameter produced by the American Academy of Child and Adolescent Psychiatry (AACAP),[70] the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) produced by expert consensus and empirical evidence,[73] the antidepressant treatment algorithm based on the Texas Children's Medication Algorithm Project (CMAP) consensus conference,[71] the clinical guideline on depression in children and young people by the National Institute for Health and Care Excellence (NICE) in the UK,[72] and the guidelines on depression in adolescents and young adults by the Australian National Health and Medical Research Council (NHMRC).[74]

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 optimizing 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]).[57]

Phases of treatment

The treatment of depression can be divided into 3 phases.

- **Acute:** lasting for 6-12 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 6-9 months; the goal of this phase is to prevent relapse. The same dose used for acute treatment should be continued. Without continuing treatment, relapse rates are very high, as demonstrated in both psychotherapy and medication studies.[1][A]Evidence 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 behavioral therapy (CBT) after acute CBT significantly lowered relapse rates compared with historical controls (6% versus 50%).[76]
- **Maintenance:** follows the continuation phase in some people; 1-2 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 pediatric depression maintenance study has been reported.[2][C]Evidence 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.

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

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 room. Hospitalization may be necessary to:
Depression in children

Treatment

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

Initial step in all patients: brief active monitoring

For uncomplicated depression, a brief period (≤4 weeks) of active monitoring, with supportive care including psychoeducation for the child and parents, is recommended. Mild depression often resolves with nonspecific treatment. Children tend to have a high placebo response.[78] It may be necessary to cut the usual period of 4 weeks of monitoring short if the symptoms are severe. If the depression becomes severe, or suicidality or psychosis develops, immediate treatment and high 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.[79] One study indicated that regular exercise significantly reduced the risk of developing dysthymia in adults.[80] Although there are no current published pediatric studies available, several pediatric depression studies are under way.

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 depression (e.g., insomnia and 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.

Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81] Antidepressants may not sufficiently resolve insomnia, so adding a sleep aid (e.g., melatonin, antihistamine) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment. In a post-hoc analysis of 2 combined studies of fluoxetine versus placebo, adolescents who reported marked insomnia showed no more improvement with fluoxetine compared with placebo, while those without insomnia showed greater benefit with fluoxetine over placebo.[82] No controlled studies have been done to show whether adding a sleep agent would improve depression treatment outcome in the pediatric population. However, in the TORDIA study, adolescents treated with trazodone were 6 times less likely to show a response to treatment compared with those not using a sleep medication, while those using other sleep medications showed similar response to adolescents not using a sleep medication.[83]

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 pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America[70] [73] and the UK.[72]

**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).

**Mild depression: inadequate improvement with active monitoring**

For mild depression that does not respond to active monitoring, a course of specific evidence-based psychotherapy, such as CBT or interpersonal psychotherapy (IPT), if available and appropriate, may be used.[84] [85] [A]Evidence CBT has also been shown to have long-term effects on prevention of depression onset.[59] [60]

In the US, if there is an inadequate response with specific psychotherapies, selective serotonin-reuptake inhibitor (SSRI) therapy may be used instead, or an SSRI could be added onto existing specific psychotherapy. Usually no further therapy is required, apart from the management of comorbid disorders and specific resistant individual symptoms, unless the depression increases in severity.

**Moderate or severe depression: inadequate improvement with active monitoring**

Specific psychotherapies may also be used for children and young people with depression of moderate or greater severity.[A]Evidence The AACAP practice parameter[70] and the GLAD-PC guidelines[57] [73] recommend any of the following approaches for young people at moderate or greater severity:

- Specific psychotherapies (e.g., CBT, IPT, dialectical behavioral therapy)
- SSRI medication
- A combination of specific psychotherapy and SSRI therapy.

If monotherapy with either specific psychotherapy or an SSRI is the initial approach, and there is an inadequate response, treatment could be augmented and continued with combined SSRI and psychotherapy.

The UK NICE guideline recommends an initial trial of psychotherapy for all young people with depression of moderate or greater severity, and recommend antidepressants only when used in conjunction with therapy.[72] The Australian NHMRC guidelines have similar recommendations but allow antidepressants when psychotherapy is not effective.[74]

In one randomized controlled trial of moderately to severely depressed adolescents, CBT plus SSRI was no more effective than SSRI alone.[87] There was no increase in disinhibition, irritability, and violence from baseline with either treatment.[87] However, long-term results and safety outcomes from one study indicate that combination therapy may decrease suicidal ideation more than medication alone.[88] 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.[89]

**SSRIs: general considerations**

SSRIs are the drug of choice, if a drug is required, and are often used after nonpharmacologic 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.[90] The Food and Drug Administration (FDA) issued a black box warning on suicidality associated with pediatric use of antidepressants in 2004.[91]

**Fluoxetine**

- The only SSRI that has >2 positive controlled trials and has positive data in both children and adolescents.[92] [93] [94] [95] This finding has been replicated in an adolescent-only trial.[96]
- In the US, fluoxetine is approved for the treatment of depression in children ages 8 to 18 years.
- Doses may be increased incrementally after initial starting regimen if there is not sufficient improvement (<50% of reduction in depression severity) of depressive symptoms.[97] Adolescents may be more likely to need a gradual increase to a higher dose than children.[98] Occasionally, fluoxetine may be increased to 60 mg daily if there is not sufficient response at other doses, especially in children or adolescents who also have comorbid anxiety disorders.
- Fluoxetine may have greater and more rapid efficacy in premenstrual dysphoric disorder.[99]
- Fluoxetine has the longest half-life of the recommended SSRIs (4-6 days), and is a potent inhibitor of cytochrome P450 enzyme 2D6 and 2C19. When concomitant medications that are metabolized 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 mother is depressed.[100]

**Escitalopram**

- In the US, escitalopram is approved for treating depression in children ages 12 to 17 years. It may be used as a first-choice antidepressant for adolescents. One trial that included children and adolescents demonstrated positive results for escitalopram over placebo in the adolescent subgroup.[101] [4[A]Evidence
- It is the active S-enantiomer of citalopram, with double the potency of citalopram. It has a half-life of 27-32 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 2 trials were pooled.[102]
- 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 1 positive trial.[103]
Depression in children

Treatment

- It has minimal effect on the P450 enzyme system, thus limited drug-to-drug interactions.

Paroxetine is not recommended for children or adolescents as first-line treatment due to lack of efficacy. It has been the subject of 3 controlled trials and all were negative, except for 1 partial positive trial in adolescents.[104] [105] [106] This medication is not effective and not well tolerated in young children; thus it is not recommended for children. It has a short half-life of 21 hours, and it is a potent inhibitor of 2B6 and 2D6 as well as a moderate inhibitor of 3A4, so drug-to-drug interactions need to be considered.

There are no pediatric 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–norepinephrine 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 individualized approach to prescribing that considers the relationship between anticipated clinical benefit and possible side effects.[90] The FDA issued a black box warning on suicidality associated with pediatric use of antidepressants in 2004.[91] Common adverse effects of SSRIs include:

- Headaches
- Nausea
- Diarrhea
- 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
- Bipolar switching
- Suicidal thoughts and behaviors.

Clinicians need to be aware of activation and bipolar switching. 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.
Suicidal thoughts and behaviors 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 behavior, both the FDA analysis and a reanalysis of all the controlled trials of antidepressant therapy have indicated an increased risk 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%).[78] [107] Eleven times more youth who are treated with an antidepressant will respond to the medication than will develop suicidal behavior.[108] It is recommended that children 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[109]
- Toronto Side Effects Scale[110]
- Liverpool University Neuroleptic Side Effects Scale[111]
- Mental Health Therapeutic Outcomes Tool.[112]

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 1-2 office visits every 4 weeks during the initial months of antidepressant treatment is required, although, in the US, the FDA recommends weekly visits during the first month after initiating an antidepressant and biweekly visits during the second and third months of therapy.

**Moderate or severe depression: inadequate improvement with first SSRI**

If, after 8 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; addition of CBT along with a switch will result in the best outcome.[113]

**Moderate or severe depression: management of inadequate response to second SSRI by switching to a non-SSRI**

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. Current evidence to support switching to a non-SSRI or augmenting is quite limited. Before initiating this step, a careful reassessment is important to verify the diagnosis, and to rule out other contributing factors, such as unrecognized or newly emergent comorbid illness (e.g., substance abuse), inadequacy of psychosocial intervention, unresolved stress, or a new trauma. If there is no indication of these factors as the cause of treatment resistance, and if a second SSRI has produced minimal to no response, switching to a non-SSRI is recommended. These agents should only be commenced by specialists who are experts in managing depression in childhood. Choices for switching include:

- Venlafaxine
- Duloxetine
- 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, emphasizing the need for a careful and individualized cost-benefit analysis prior to considering treatment.[90]

Venlafaxine

An SNRI. To assess the efficacy of this treatment, 3 controlled studies have been conducted, and all were negative. However, when the data from 2 studies was pooled together, the adolescent subgroup showed that venlafaxine was superior compared with placebo in reducing depression.[114] [115] 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.[116] In the FDA assessment, compared with other antidepressants, venlafaxine did have significantly more suicide-related adverse events than placebo.[107] A retrospective cohort study of 36,842 patients ages 6 to 18 years showed no evidence that risk of suicide attempts differed for SSRI and SNRI antidepressants.[117] Extended-release formula is recommended, which still has a relatively short half-life of 10.3 hours.

Duloxetine

Also an SNRI. A negative trial has been published.[118] Unlike venlafaxine, which does not significantly influence the P450 enzyme system, duloxetine is a potent inhibitor of 1A2 and 2D6. It has a similarly short half-life of 12.5 hours.

Mirtazapine

A serotonin receptor 2 (5-HT2) antagonist, with a half-life of 20-40 hours. The only 2 multicenter pediatric mirtazapine trials were negative, possibly due to the high placebo response in the 2 studies.[119] 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.[91]

Nefazodone

There is one positive trial but the medication is not marketed for children due to hepatotoxicity (though risk is low).

**Moderate or severe depression: management of inadequate response to second SSRI by augmentation strategies**

An alternate 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,[120] triiodothyronine,[122] atypical antipsychotic medications,[124] and bupropion[126] have been studied most frequently, with some indications of efficacy. Atypical antipsychotics and bupropion have been used more frequently in the pediatric population as augmenting agents compared with other agents. However, pediatric 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 pediatric treatment-resistant depression found that adolescents who had more than 9 CBT sessions in additional to treatment with a second SSRI or venlafaxine were more likely to have a positive response than adolescents who received fewer CBT sessions.[127]

Bupropion is one of the more frequently used augmenting agents, although no pediatric 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.[128] More studies have been completed in bipolar depression.

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 2 open pediatric trials also used lithium to augment a TCA.[129] [130] Blood levels need to be monitored to avoid toxicity. Thyroid and renal function also need to be monitored regularly.

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

**Novel alternative approaches for children with treatment-resistant depression**

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])
- Emerging therapies (e.g., the transdermal selegiline patch), as part of a clinical trial.

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 pediatric depression, and tend to produce more adverse events.[131] Because of the adverse effects and the difficulty of managing diet in children and adolescents, MAOIs have not been recommended for use in pediatric depression. However, the patch form of a selective MAOI, selegiline, may bypass the concern and
Depression in children

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% versus 59.3%).[132]

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.[133] A recent review and meta-analysis indicates that light therapy may be effective for nonseasonal depression in adults.[134]

Case reports on the efficacy of ECT in pediatric depression have appeared for more than 60 years.[135] However, there have not been any controlled trials conducted in the pediatric 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 CAM is used frequently around the world for treating pediatric depression, including in the US, there is extremely limited empiric evidence for its efficacy.[136] The 2005 UK NICE guideline opposes the use of St. John's wort in children, due to insufficient evidence of efficacy and known drug interactions. Other guidelines (AACAP, CMAP, GLAD-PC, Australian NHMRC) have not discussed the use of natural remedies in the management of pediatric 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.[137] There are many adult-controlled studies that indicate inconsistent efficacy in treating adult depression.[138] [139] No controlled studies have been conducted in depressed children. 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.[140] [141] [142] 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.[143] 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.[144] 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, norepinephrine, and dopamine. Adult depression trials of SAMe indicated superior efficacy to placebo and comparable efficacy to TCAs.[145] SAMe may also be effective as an augmenting agent.[146] No pediatric depression studies are available, except for case reports that indicate efficacy in treating depression in children and adolescents.[147] Interactions of SAMe with other medications appear to be infrequent.[139]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

<table>
<thead>
<tr>
<th>Initial</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk of harm to themselves or others</td>
<td>1st urgent emergency admission and mental healthcare assessment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>1st active monitoring + supportive care</td>
</tr>
<tr>
<td>adjunct</td>
<td>management of associated symptoms and comorbid disorders</td>
</tr>
<tr>
<td>2nd</td>
<td>specific psychotherapy + supportive care</td>
</tr>
<tr>
<td>adjunct</td>
<td>management of associated symptoms and comorbid disorders</td>
</tr>
<tr>
<td>3rd</td>
<td>switch to or add on selective serotonin-reuptake inhibitor (SSRI) + continued supportive care</td>
</tr>
<tr>
<td>adjunct</td>
<td>management of associated symptoms and comorbid disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>moderate or severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
</tr>
<tr>
<td>adjunct</td>
</tr>
<tr>
<td>2nd</td>
</tr>
<tr>
<td>adjunct</td>
</tr>
</tbody>
</table>
### Acute

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Management of associated symptoms and comorbid disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd psychotherapy + supportive care</td>
<td></td>
</tr>
<tr>
<td>Adjunct</td>
<td>Selective serotonin-reuptake inhibitor (SSRI)</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Management of associated symptoms and comorbid disorders</td>
</tr>
<tr>
<td>3rd</td>
<td>Switch to a different selective serotonin-reuptake inhibitor (SSRI) + supportive care</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Management of associated symptoms and comorbid disorders</td>
</tr>
<tr>
<td>4th</td>
<td>Switch to a non-selective serotonin-reuptake inhibitor (SSRI) + supportive care</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Management of associated symptoms and comorbid disorders</td>
</tr>
<tr>
<td>4th</td>
<td>Augmentation of second selective serotonin-reuptake inhibitor (SSRI) with psychotherapy or with another medication + supportive care</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Management of associated symptoms and comorbid disorders</td>
</tr>
<tr>
<td>5th</td>
<td>Novel alternative approaches + supportive care</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Management of associated symptoms and comorbid disorders</td>
</tr>
</tbody>
</table>

### Ongoing

Following stabilization of acute symptoms

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Management of associated symptoms and comorbid disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Continuation therapy for 6-12 months</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Maintenance therapy for 1-2 years</td>
</tr>
</tbody>
</table>
## Treatment options

### Initial

<table>
<thead>
<tr>
<th>at risk of harm to themselves or others</th>
<th>1st urgent emergency admission and mental healthcare assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» 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 room.</td>
</tr>
<tr>
<td></td>
<td>» Hospitalization may be necessary to carry out an urgent mental healthcare assessment; ensure safety for the patient and/or for others; and stabilize the patient.</td>
</tr>
</tbody>
</table>

### Acute

<table>
<thead>
<tr>
<th>mild</th>
<th>1st active monitoring + supportive care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» For mild and uncomplicated depression, a brief period (up to 4 weeks) of active monitoring, with supportive care including psychoeducation for the child and parents, is recommended. Mild depression often resolves with nonspecific treatment. Children tend to have a high placebo response.[78]</td>
</tr>
<tr>
<td></td>
<td>» 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 pediatric evidence is still limited.[79]</td>
</tr>
<tr>
<td></td>
<td>» 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.</td>
</tr>
</tbody>
</table>

adjunct management of associated symptoms and comorbid disorders

**Primary options**

- melatonin: children: 1-3 mg orally once daily at bedtime

OR

...
Depression in children

### Treatment

#### Acute

- **diphenhydramine**: children ≥ 6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day

  OR

- **hydroxyzine**: children: 25-50 mg orally once daily at bedtime

  » Comorbidities such as ADHD and anxiety may require specific treatment. In addition, some depressive symptoms (e.g., insomnia, agitation) may take a long time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

  » Insomnia is a frequent symptom of depression and also a frequent residual symptom.°

  Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

  » Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [70] the UK,[72] and Australia.[74]

#### 2nd specific psychotherapy + supportive care

- If the response to active monitoring is inadequate, a course of specific evidence-based psychotherapy, such as cognitive behavioral therapy or interpersonal psychotherapy, if available and appropriate, may be used.[84] [85] 3[A]Evidence

- 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

- **melatonin**: children: 1-3 mg orally once daily at bedtime

  OR

- **comparative**

  - **venlafaxine**: children: 15 mg orally once daily at bedtime

  - **paroxetine**: children: 20 mg orally once daily at bedtime
### Acute

- **diphenhydramine**: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day
  
  OR

- **hydroxyzine**: children: 25-50 mg orally once daily at bedtime

- Comorbidities such as ADHD and anxiety may require specific treatment. In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so some patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression, and also a frequent residual symptom.[81] Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

- Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] the UK,[72] and Australia.[74]

### 3rd switch to or add on selective serotonin-reuptake inhibitor (SSRI) + continued 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: 5-10 mg orally once daily initially, increase according to response, maximum 30 mg/day
Depression in children

Treatment

Acute

» sertraline: 12.5 to 25 mg orally once daily initially, increase according to response, maximum 200 mg/day

OR

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

» If the response to active monitoring and specific psychotherapy is inadequate, an SSRI may be initiated. This may be given as a monotherapy, or may be used in addition to specific psychotherapies. Use of SSRIs for mild depression at this stage is not unusual in the US, but may not be recommended in other countries.

» 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, emphasizing the need for a careful and individualized cost-benefit analysis prior to treatment. [90]

» The Food and Drug Administration (FDA) has issued warnings that the use of antidepressant medications poses a small, but significantly increased, risk of suicidal ideation or suicide attempts for children and adolescents.

» A minimum of 1-2 office visits every 4 weeks during the initial months of antidepressant treatment is required, although the FDA recommends weekly visits during the first month after initiating an antidepressant, and biweekly visits during the second and third months of therapy.

» 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.

» Some of the pediatric doses given below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]
## Acute

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

### Primary options

- **» melatonin**: children: 1-3 mg orally once daily at bedtime  
- **OR**
- **» diphenhydramine**: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day  
- **OR**
- **» hydroxyzine**: children: 25-50 mg orally once daily at bedtime  

- Comorbidities such as ADHD and anxiety may require specific treatment. 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.

- In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive therapies are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81]  
Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

- Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]

## moderate or severe

**1st** active monitoring + supportive care

- For uncomplicated depression, a brief period (≤4 weeks) of active monitoring with psychoeducation and supportive therapy is recommended. It may be necessary to cut the
### Treatment

**Depression in children**

<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>usual period of 4 weeks of monitoring short if the symptoms are severe.</td>
</tr>
</tbody>
</table>

- 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 pediatric evidence is still limited.[79]

- 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**

**Primary options**

- **melatonin**: children: 1-3 mg orally once daily at bedtime

OR

- **diphenhydramine**: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day

OR

- **hydroxyzine**: children: 25-50 mg orally once daily at bedtime

- Comorbidities such as ADHD and anxiety may require specific treatment. In addition, some depressive symptoms (e.g., insomnia, agitation) may take longer to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive therapies are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81] Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

- Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a
### Acute

**TREATMENT**

<table>
<thead>
<tr>
<th>2nd</th>
<th>specialise experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]</th>
</tr>
</thead>
</table>

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

**Primary options**

- **flutoxetine**: 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

- **escitalopram**: children <12 years of age: consult specialist for guidance on dose; children ≥12 years of age: 5-10 mg orally once daily initially, increase according to response, maximum 30 mg/day

- **sertraline**: 12.5 to 25 mg orally once daily initially, increase according to response, maximum 200 mg/day

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

- For moderate or severe depression that does not respond to active monitoring, antidepressant treatment with an SSRI may be initiated.

- The American Academy of Child and Adolescent Psychiatry’s practice parameter and the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) guidelines recommend either specific psychotherapies, medication, or their combination for young people at moderate or greater severity.[73] The UK National Institute for Health and Care Excellence guidelines recommend an initial trial of psychotherapy, and recommend antidepressants only when used in conjunction with therapy.[72] The Australian National Health and Medical Research Council's guidelines recommend antidepressants when depression is severe or when psychotherapy is not effective, not available, or refused.[74]
Depression in children

**Acute**

» 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, emphasizing the need for a careful and individualized cost-benefit analysis prior to treatment.[90]

» The Food and Drug Administration (FDA) has issued warnings that use of antidepressant medications poses a small, but significantly increased, risk of suicidal ideation or suicide behavior for children and adolescents.

» A minimum of 1 to 2 office visits every 4 weeks during the initial months of antidepressant treatment is required, although, in the US, the FDA recommends weekly visits during the first month after initiating an antidepressant, and biweekly visits during the second and third months of therapy.

» 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.

» Some of the pediatric doses given below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]

adjunct psychotherapy

» If monotherapy with a selective serotonin-reuptake inhibitor (SSRI) leads to an inadequate response, treatment could be augmented and continued with combined SSRI and psychotherapy.

adjunct management of associated symptoms and comorbid disorders

**Primary options**

» melatonin: children: 1-3 mg orally once daily at bedtime

OR
### Acute

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- diphenhydramine: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- hydroxyzine: children: 25-50 mg orally once daily at bedtime</td>
</tr>
</tbody>
</table>

- Comorbidities such as ADHD and anxiety may require specific treatment. 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.

- In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81] Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

- Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] the UK,[72] and Australia.[74]

### 2nd psychotherapy + supportive care

- For moderate or severe depression that does not respond to active monitoring, the American Academy of Child and Adolescent Psychiatry's practice parameter and the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) guidelines recommend either specific psychotherapies, medication, or their combination for young people at moderate or greater severity.[73] The UK National Institute for Health and Care Excellence guidelines recommend an initial trial of psychotherapy, and recommend antidepressants only when used in conjunction with therapy.[72] The Australian National Health and Medical Research Council's guidelines recommend antidepressants when...
Acute depression is severe or when psychotherapy is not effective, not available, or refused.[74]

» 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 selective serotonin-reuptake inhibitor (SSRI)

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: 5-10 mg orally once daily initially, increase according to response, maximum 30 mg/day

OR

» sertraline: 12.5 to 25 mg orally once daily initially, increase according to response, maximum 200 mg/day

OR

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

» If monotherapy with specific psychotherapy leads to an inadequate response, treatment could be augmented and continued with combined SSRI and psychotherapy.

» 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, emphasizing the need for a careful and individualized cost-benefit analysis prior to treatment.[90]
Depression in children

**Treatment**

### Acute

- The Food and Drug Administration (FDA) has issued warnings that the use of antidepressant medications poses a small, but significantly increased, risk of suicidal ideation or suicide attempts for children and adolescents.

- A minimum of 1 to 2 office visits every 4 weeks during the initial months of antidepressant treatment is required, although, in the US, the FDA recommends weekly visits during the first month after initiating an antidepressant, and biweekly visits during the second and third months of therapy.

- Some of the pediatric doses given below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]

### Adjunct management of associated symptoms and comorbid disorders

**Primary options**

- **Melatonin**: children: 1-3 mg orally once daily at bedtime

  OR

- **Diphenhydramine**: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day

  OR

- **Hydroxyzine**: children: 25-50 mg orally once daily at bedtime

- Comorbidities such as ADHD and anxiety may require specific treatment. 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.

- In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81]
### Treatment

#### Acute

<table>
<thead>
<tr>
<th>3rd switch to a different selective serotonin-reuptake inhibitor (SSRI) + supportive care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td>» fluoxetine: children &lt;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</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» escitalopram: children &lt;12 years of age: consult specialist for guidance on dose; children ≥12 years of age: 5-10 mg orally once daily initially, increase according to response, maximum 30 mg/day</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» sertraline: 12.5 to 25 mg orally once daily initially, increase according to response, maximum 200 mg/day</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>» citalopram: 10 mg orally once daily initially, increase according to response, maximum 40 mg/day</td>
</tr>
</tbody>
</table>

» 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 behavioral therapy.

» The results of one meta-analysis suggest that SSRIs are more beneficial than placebo for treating children and adolescents with...
## Treatment

### Acute

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, emphasizing the need for a careful and individualized cost-benefit analysis prior to treatment.[90]

- The Food and Drug Administration (FDA) has issued warnings that the use of antidepressant medications poses a small, but significantly increased, risk of suicidal ideation or suicide attempts for children and adolescents.

- A minimum of 1 to 2 office visits every 4 weeks during the initial months of antidepressant treatment is required, although, in the US, the FDA recommends weekly visits during the first month after initiating an antidepressant, and biweekly visits during the second and third months of therapy.

- 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.

- Some of the pediatric doses given below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [70] the UK,[72] and Australia.[74]

### Adjunct Management of Associated Symptoms and Comorbid Disorders

#### Primary Options

- **Melatonin**: children: 1-3 mg orally once daily at bedtime

OR

- **Diphenhydramine**: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day

OR

- **Hydroxyzine**: children: 25-50 mg orally once daily at bedtime

- Comorbidities such as ADHD and anxiety may require specific treatment. It is not...
**Acute**

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.

- In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81] Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

- Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]

**4th switch to a non-selective serotonin-reuptake inhibitor (SSRI) + supportive care**

### Primary options

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

OR

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

OR

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

OR

- **bupropion hydrochloride:** 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 unrecognized or newly emergent comorbid illness (e.g., substance abuse), inadequacy of...**
### Acute

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 venlafaxine, duloxetine, mirtazapine, and bupropion. These agents should only be commenced by specialists who are experts in managing depression in childhood.

- The results of one meta-analysis suggest that serotonin–norepinephrine 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, emphasizing the need for a careful and individualized cost-benefit analysis prior to considering treatment.[90]

- Venlafaxine did have significantly more suicide-related adverse events than placebo in one assessment.[107]

- 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.

- Some of the pediatric doses given below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] the UK,[72] and Australia.[74]

### Adjunct Management of Associated Symptoms and Comorbid Disorders

**Primary options**

- **Melatonin**: children: 1-3 mg orally once daily at bedtime

  OR

- **Diphenhydramine**: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day

  OR
Depression in children

**Treatment**

**Acute**

- **hydroxyzine**: children: 25-50 mg orally once daily at bedtime

- Comorbidities such as ADHD and anxiety may require specific treatment. 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.

- In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81] Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

- Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders. Guidelines for prescribing are available for North America,[73] [70] the UK,[72] and Australia.[74]

**4th augmentation of second selective serotonin-reuptake inhibitor (SSRI) with psychotherapy or with another medication + 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: 5-10 mg orally once daily initially, increase according to response, maximum 30 mg/day
  - or-
  - **sertraline**: 12.5 to 25 mg orally once daily initially, increase according to response, maximum 200 mg/day
  - or-
## Acute

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

---

**AND**

- **psychotherapy**
- **bupropion hydrochloride**: consult specialist for guidance on dose
- **quetiapine**: consult specialist for guidance on dose
- **aripiprazole**: consult specialist for guidance on dose
- **ziprasidone**: consult specialist for guidance on dose
- **risperidone**: consult specialist for guidance on dose
- **olanzapine**: consult specialist for guidance on dose
- **lamotrigine**: consult specialist for guidance on dose
- **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 unrecognized or newly emergent comorbid illness (e.g., substance abuse), 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 pediatric population as augmenting agents, compared with other agents. However, pediatric 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.
Depression in children

TREATMENT

<table>
<thead>
<tr>
<th>Acute</th>
<th>Management of associated symptoms and comorbid disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Some of the pediatric doses given below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]</td>
</tr>
</tbody>
</table>

**Primary options**

- melatonin: children: 1-3 mg orally once daily at bedtime

  OR

- diphenhydramine: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day

  OR

- hydroxyzine: children: 25-50 mg orally once daily at bedtime

  » Comorbidities such as ADHD and anxiety may require specific treatment. 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.

  » In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

  » Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81] Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

  » Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [70] the UK,[72] and Australia.[74]
Depression in children

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>novel alternative approaches + supportive care</td>
</tr>
</tbody>
</table>

» 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 selective serotonin-reuptake inhibitors (SSRIs) or non-SSRIs. TCAs have not been shown to be effective in treating pediatric depression, and tend to produce more adverse events.[131]

Because of the adverse effects and difficulty of managing diet in children and adolescents, MAOIs have not been recommended for use in pediatric depression. However, the transdermal patch formulation of the MAOI selegiline may bypass the concern, and become an alternative treatment for young people with depression resistant to other treatment.[132]

» Biological treatments include light therapy and electroconvulsive therapy (ECT). There have not been any controlled trials of ECT conducted in the pediatric 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

Primary options

» melatonin: children: 1-3 mg orally once daily at bedtime

OR

» diphenhydramine: children ≥6 months of age: 1 mg/kg orally once daily at bedtime, maximum 50 mg/day

OR

» hydroxyzine: children: 25-50 mg orally once daily at bedtime
Depression in children

**Acute**

- Comorbidities such as ADHD and anxiety may require specific treatment. 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.

- In addition, some depressive symptoms (e.g., insomnia, agitation) may take a longer time to resolve, so certain patients may need adjunctive treatment early on during the acute treatment phase. Adjunctive treatments are discontinued when the target symptom resolves.

- Insomnia is a frequent symptom of depression and also a frequent residual symptom.[81] Sleep-enhancing medications (e.g., melatonin, antihistamines) or using an evidence-based psychosocial intervention for insomnia may be helpful to resolve insomnia early during acute treatment.

- Some of the drugs recommended below are considered off-label in some countries. These drugs are only to be prescribed by a specialist experienced in the treatment of pediatric psychiatric disorders in those countries. Guidelines for prescribing are available for North America,[73] [148] the UK,[72] and Australia.[74]

**Ongoing**

following stabilization of acute symptoms

<table>
<thead>
<tr>
<th>1st</th>
<th>continuation therapy for 6-12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>adjunct</th>
<th>maintenance therapy for 1-2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» 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).</td>
</tr>
<tr>
<td></td>
<td>» One small pediatric depression maintenance study has been reported.[2(C)Evidence] Although a larger study is needed, maintenance treatment is recommended by treatment guidelines.</td>
</tr>
</tbody>
</table>
Emerging

Transcranial magnetic stimulation (TMS)

There is emerging evidence that repetitive TMS (rTMS) maybe safe and effective for treating depression in adolescents.[149][150]

Vagus nerve stimulation (VNS)

There is evidence to support the use of VNS in adult treatment-resistant depression.[151][152][153] However, there have been no trials for pediatric depression. Because of the invasive nature of the procedure and potential adverse effects, it is not recommended for use in treating pediatric 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 pediatric 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%).[132]

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.[154] 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.[155] No pediatric 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.[156] A systematic review of 60 articles looking at side effects in adults with depression treated with single and repeated doses of ketamine found that acute side effects were common, and were more likely to occur in patients given intravenous ketamine. The majority of side effects resolved shortly after drug administration. They included psychiatric (most commonly anxiety), psychotomimetic, cardiovascular, and neurologic effects. The most common 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 urologic and liver toxicity, cognitive deficits, and dependency. Ketamine dependency is a known disorder.[157] 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 norepinephrine) have been investigated. Studies have found that agomelatine (a melatonin receptor agonist and serotonin 2c receptor antagonist) surpassed placebo[158] and fluoxetine[159] in reducing depression severity and improving sleep, and sertraline in regulating the circadian rest-activity, sleep-wake cycle, and in reducing depressive and anxiety symptoms[160] and preventing relapse in depressed adults.[161]

Exercise

A meta-analyses has suggested that exercise is effective in treating major depressive disorder in adults.[162] and several trials are under way to assess the efficacy of exercise in treating pediatric depression.
**Recommendations**

**Monitoring**

After treatment is initiated, weekly to biweekly 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.[73] 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.[165] 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.

**Patient instructions**

Education of the parents and child about depression is important. It is important to explain to the patient and caregiver 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 pediatrician, family doctor, child psychiatrist, or a counselor 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 with 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.

**Complications**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment-induced mania, agitation, or disinhibition</td>
<td>short term</td>
<td>low</td>
</tr>
</tbody>
</table>

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 behavior | variable   | low       |
Depression in children

Complications | Timeframe | Likelihood
--- | --- | ---
Suicidal ideation occurs more frequently than suicidal behavior and suicide attempts in young people with depressive disorder. However, depression is the most frequent psychiatric illness among suicide completers.[164] Suicidal thoughts and behaviors may occur prior to or during treatment.

There is not sufficient evidence to support the suggestion that antidepressants could cause suicidality. There is a slight increased risk of suicidality (1%-2%) associated with antidepressant use (3%-4%) compared with placebo (2%).[78] [107] The Food and Drug Administration issued a black box warning on suicidality associated with pediatric use of antidepressants in 2004.[91]

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.

<table>
<thead>
<tr>
<th>aggression</th>
<th>variable</th>
<th>low</th>
</tr>
</thead>
</table>

Children and adolescents with depressive disorder may be irritable and angry. Childhood depression is also highly comorbid with disruptive behavior disorders. Occasionally, antidepressants may increase agitation.

Careful assessment of irritability, anger, and aggressive behavior, 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.

<table>
<thead>
<tr>
<th>substance abuse</th>
<th>variable</th>
<th>low</th>
</tr>
</thead>
</table>

Depression increases the risk of substance abuse.[70] If a child is not responding to treatment, a concurrent use or abuse of a substance needs to be ruled out.

Questions about substance use need to be asked routinely, and a drug screen may need to be administered if there is any indication of substance abuse, particularly in adolescents.

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.[70] About 50% to 60% of young people respond to first psychotherapy or medication treatment. Between 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.[116] 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. Up to 70% of young people have a recurrence of an episode within 5 years of 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 abuse.[70] 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 which predated the introduction of diagnostic criteria.)[163]
## Diagnostic guidelines

### International

**Guidelines for adolescent depression in primary care (GLAD-PC): Part I. Practice preparation, identification, assessment, and initial management**


**Screening for depression in children and adolescents: US Preventive Services Task Force recommendation statement**


**Practice parameter for the assessment and treatment of children and adolescents with depressive disorders**


**Texas children's medication algorithm project (CMAP)**


**Depression in children and young people: identification and management**


Published by: American Academy of Pediatrics
Last published: 2018

Published by: American Academy of Child and Adolescent Psychiatry
Last published: 2007

Published by: Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder
Last published: 2007

Published by: National Institute for Health and Care Excellence (UK)
Last published: 2017
Clinical practice guidelines: depression in adolescents and young adults

Published by: Australian National Health and Medical Research Council; beyondblue (The National Depression Initiative)  
Last published: 2011
Online resources

1. Duke University: Mood and Feelings Questionnaire (external link)
Evidence scores

1. **Relapse rate**: there is good-quality evidence that children and adolescents (ages 7-18 years) with major depressive disorder who continue therapy with a further 6 months of fluoxetine, having responded to an initial 12 weeks of fluoxetine, had lower relapse rates (42.0%) compared with those continued on placebo (69.2%).[75]
   
   **Evidence level A**: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

2. **Relapse in the maintenance phase**: there is poor-quality evidence that 38% of adolescents with major depressive disorder who received a further 52 weeks of maintenance treatment with sertraline, following initial response to sertraline in the acute and continuation phases, remained well, compared with none of the adolescents randomized to placebo for the maintenance phase.[77]
   
   **Evidence level C**: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

3. **Treatment efficacy**: there is good-quality evidence that there is a small average effect size (0.34, SD = 0.40, ranging -0.66 to 2.02) for evidence-based youth psychotherapies used to treat depression in young people.[86]
   
   **Evidence level A**: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

4. **Reduction in depression scores**: there is good-quality evidence that escitalopram is significantly more effective than placebo in reducing depression scores in adolescents with major depressive disorder.[96]
   
   **Evidence level A**: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.
Key articles


References


<table>
<thead>
<tr>
<th>Reference</th>
<th>Title and Authors</th>
</tr>
</thead>
</table>


Abstract

Abstract

Abstract

Full text  
Abstract

Full text  
Abstract

Abstract

Full text  
Abstract

Abstract

Full text  
Abstract

Abstract

Abstract

Full text  
Abstract


112. Chehil S, Kutcher S. Mental health therapeutic outcomes tool (TOT). 2007 [internet publication]. Full text


Depression in children

References


<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
</tr>
</thead>
</table>
Disclaimer

This content is meant for medical professionals. The BMJ Publishing Group Ltd (“BMJ Group”) tries to ensure that the information provided is accurate and up-to-date, but we do not warrant that it is. The BMJ Group does not advocate or endorse the use of any drug or therapy contained within nor does it diagnose patients. Medical professionals should use their own professional judgement in using this information and caring for their patients and the information herein should not be considered a substitute for that.

This information is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. We strongly recommend that users independently verify specified diagnosis, treatments and follow up and ensure it is appropriate for your patient. This information is provided on an “as is” basis and to the fullest extent permitted by law the BMJ Group assumes no responsibility for any aspect of healthcare administered with the aid of this information or any other use of this information.

View our full Website Terms and Conditions.

Contact us

+1 855-458-0579 (toll free from USA)
ussupport@bmj.com

BMJ Americas Office
2 Hudson Place, Suite 300
Hoboken, New Jersey 07030
Contributors:

// Authors:

Lisa Pan, MD
Assistant Professor of Psychiatry and Clinical and Translational Science
University of Pittsburgh, Attending Physician, Services for Teens at Risk, Pittsburgh, PA
DISCLOSURES: LP declares that she has no competing interests.

David A. Brent, MD
Endowed Chair in Suicide Studies
Professor of Psychiatry, Pediatrics, Epidemiology, and Clinical and Translational Science, University of Pittsburgh, PA
DISCLOSURES: DAB receives royalties from Guilford Press; has received or will receive royalties from the electronic self-rated version of the C-SSRS from ERT, Inc; is on the editorial board of UpToDate; is a reviewer for Healthwise; and is on the board of the Klingenstein Foundation.

// Acknowledgements:

Dr Lisa Pan and Dr David A. Brent would like to gratefully acknowledge Dr Rongrong Tao, Dr Graham Emslie, and Dr Taryn Mayes, the previous contributors to this topic. RT is an author of a number of references cited in this topic. GE has received research funds from BioMarin, Eli Lilly, Forest Laboratories, GlaxoSmithKline, and Somerset; has served as a consultant for Biobehavioral Diagnostic Company, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, INC Research Inc., Lundbeck, Pfizer Inc., Seaside Therapeutics, Shire Pharmaceuticals, Valeant, Validus Pharmaceuticals, and Wyeth Ayerst; and has been on the speaker's bureau for Forest Laboratories. TM is an author of a number of references cited in this topic.

// Peer Reviewers:

Paramala J. Santosh, MBBS, DipNB (Psych), MRCPsych, MD
Honorary Senior Lecturer
Institute of Child Health and Institute of Psychiatry, Consultant in Child and Adolescent Neuropsychiatry and Psychopharmacology, Head of Centre for Interventional Paediatric Psychopharmacology, Department of Child & Adolescent Mental Health, Great Ormond Street Hospital for Children, London, UK
DISCLOSURES: PJS declares that he has no competing interests.

Pieter Joost van Wattum, MD, MA
Assistant Clinical Professor of Child Psychiatry
Yale School of Medicine, Medical Director of Psychiatry, Clifford W. Beers Guidance Clinic, New Haven, CT
DISCLOSURES: PJvW declares that he has no competing interests.