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Introduction

Depression is the leading cause of disability worldwide, contributing to underperformance in school, decline in productivity, and disruption of family functioning [1]. Adolescence is the period of highest risk for onset of depression with peak incidence in the United States in the early 20s [1, 2]. Depression is generally a chronic episodic condition, which at its worst can lead to suicide, the leading cause of death in individuals ages 15–29 worldwide [1, 2]. Individuals with depression can experience low mood, decline in interests, low energy, disturbances in sleep and appetite, and feelings of hopelessness. In children and adolescents, depression may be associated with changes in behavior, such as irritability, social withdrawal, and somatic complaints [3].

The spectrum of depressive disorders include major depressive disorder, persistent depressive disorder (formerly known as dysthymia), and depressive disorder related to substance use or a medical condition, among other categorizations [3, 4]. Over the last 30 years, safe effective treatments for depression have become increasingly available; therefore, screening, identification, and early treatment are important public health efforts. Signs and symptoms of depression can often go unnoticed or mischaracterized. This, among other factors such as social stigma and limited access to mental health services, can delay or deter adequate treatment.

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Brief Review of Epidemiology and Pathophysiology

The overall prevalence of depression in the United States by the age of 18 is about 20% [3]. In children, the prevalence of major depressive disorder (MDD) is about 2%, and in adolescents it is about 4–8% [5]. It is estimated that another 5–10% of children and adolescents have symptoms of MDD that fall below the threshold for full diagnostic criteria; however, they are at elevated risk for suicide [5]. Depression occurs equally across genders in children, but in adolescence, the risk for developing depression increases for females, with a female to male ratio of 2:1 [5].

Risk factors for depression can be characterized by a biopsychosocial framework. Biologically, it has been shown that first-degree family members of individuals with MDD have a two- to fourfold risk of developing depression compared to the general population [6]. Additionally, the presence of other parental psychiatric disorders, including anxiety, substance abuse, ADHD, and eating disorders, has been associated with the development of depression in children and adolescents. Experiences of stressful life events, such as abuse, neglect, exposure to violence, and family disruption, in childhood have also been associated with the onset of MDD [7, 8]. The effects of these experiences are often mediated by the child's sources of support, socioeconomic status, IQ, and coping style [9].

The course of depression can range from 3 to 8 months [10]. About one in five adolescents has persistent depression that can last 2 years or more [10]. Recurrence after remission of symptoms is common with an estimated 20–60% of children and adolescents experiencing a recurring episode of depression in 1–2 years and 70% over 5 years [11, 12]. Additionally, it is estimated that 40–90% of children and adolescents with depression also have another psychiatric disorder. The most common comorbid conditions include anxiety disorders, attention deficit hyperactivity disorder, and disruptive behavior disorders. In adolescents, substance abuse disorders commonly occur with depression [4].

Diagnosis and Key Components of History

The DSM5 lists major depressive disorder within the category of depressive disorders and describes “The common feature of all of these depressive disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. What differs among them are issues of duration, timing, or presumed etiology” [2]. Individuals meet criteria for major depressive disorder if they have depressed mood or loss of interest along with five or more of the following symptoms for 2 weeks [2]:

1. Depressed mood
2. Lack of interest or pleasure in all or most activities
3. Unexpected changes in weight (for children, failure to gain weight as expected)
4. Sleep disturbance (insomnia or hypersomnia)
5. Feeling of slowing or agitation

6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate or indecisiveness
9. Recurrent thoughts of death or suicidal ideation

Major depressive disorder can be a pervasive and debilitating disorder that impacts an individual's view of the world, themselves, and others [13, 14]. Depression in children and adolescents is also associated with negative attributions that impact feelings about self-worth and abilities (e.g., self-esteem), interactions with others (e.g., isolation or anger), and views of the world and the future (e.g., helplessness, foreshortened future) [15–17]. For depressed children, negative attributions and depressed mood can increase over time, particularly during adolescence; therefore it is important for healthcare professionals to be able to identify and treat early when possible [16, 18].

Assessment of severity is necessary for determining relevant psychoeducation, appropriate monitoring, and next steps. Screeners such as the Patient Health Questionnaire for Adolescents (PHQ-A) that assess presence and level of symptoms are useful for assessing severity [19]. Symptoms may fall in the mild, moderate, or severe range. The child with mild severity (PHQ-A score 5–9) may exhibit few symptoms or low levels of symptoms that may or may not noticeably impair daily functioning. Mild symptoms may or may not require treatment beyond primary care. The child with moderate severity (PHQ-A score 10–14) may exhibit several symptoms that impact functioning and may likely require further evaluation and treatment. The child with severe symptoms (PHQ-A score 20–27) may exhibit many symptoms at high levels that clearly negatively impact daily functioning and likely require specialty treatment, monitoring, and follow-up. PHQ-9 scores ≥ 10 have a sensitivity of 88% and a specificity of 88% for major depression [19].

It is important to remember that depression may be exhibited differently in children than in adolescents or young adults. While adolescent depression is more common, it is important to be aware that young children (e.g., under age 10) can show signs of depression, especially when risk factors such as parental depression are present [16, 18]. While adolescents and young adults may exhibit sad mood associated with depressive symptoms, younger children may express negative mood by displaying other types of behaviors. This may include irritable behaviors (misbehavior, anger, tantrums) instead of/or in addition to sad behaviors (tearfulness and low mood). Directly asking about suicide attempts and thoughts of wanting to die is particularly important for depressed adolescents and teens (e.g., “Have you ever had thoughts of wanting to hurt or kill yourself?” “Have you ever tried to hurt or kill yourself?”) [19]. Whereas teenage girls make more suicide attempts, teenage boys are more likely to complete suicide [19, 20]. Rates are higher among Native American, White, and Hispanic teens than among Black, Asian, or teens from Pacific Islands [20].

There are variations in reporting of depressive symptoms by gender and ethnicity [21]. While prepubescent males and females tend to have equal prevalence rates of depression, girls begin to report more depressive symptoms than boys after puberty.

Table 10.1 Key questions during assessment

Behavior topics: sleep, appetite, social withdrawal/isolation, tearfulness, concentration, tantrums/misbehavior	Is the child spending less time with friends than before? Is the child spending less time doing activities they used to enjoy? Have you noticed changes in their appetite? Have you noticed changes in their sleep? Does the child appear more tired than usual? (For older children, ask if they seem to take more naps)
Mood topics: irritable, sad, angry, flat, sluggish/lethargic	Does the child seem angry or easily frustrated? Does the child seem easily tearful? Does the child seem to have less energy than before?
Thought topics: suicide, low self-esteem, failure	Is the child hard on themselves or expressing statements about failure or worthlessness? Does the child express statements about wanting to die?
Social environment topics: changes/transitions, stressors, major losses, school, peers	Have there been any recent changes or transitions you can think of, such as moving, changing schools, etc.? Have there been any recent losses, deaths, or anniversaries? How are the child's grades/have there been changes in grades or completion of school work? Are there concerns about bullying or being bullied?

Healthcare providers should be aware of biological and social/contextual reasons for these variations and continue to listen carefully to how more “acceptable” symptoms may be described by patients and families (e.g., angry or bored versus sad). Research on mental health disparities shows that ethno-cultural minority children are frequently underserved and misdiagnosed relative to their white counterparts [21–23]. Research suggests cultural differences in reporting of symptoms, where families from ethno-cultural minority groups may underreport depressive symptoms. Nevertheless, it is crucial for healthcare providers to listen carefully, clarify concerns, minimize blame, and seek accurate diagnosis. For example, parental concerns about “laziness, missed chores, and failing grades” may also be an expression of concerns about anhedonia and low mood.

Key areas to ask about for assessment including behavior, mood, thoughts, and social environment are included in Table 10.1.

This list is not an exhaustive account of which questions to ask but is intended to provide some direction in the assessment of pediatric depression. Consequently, taken individually the above symptoms could also be indicative of other disorders, but taken together it is likely that the child is exhibiting symptoms of depression.

It is also important to note how long symptoms have been present, when they were first noticed, and how much trouble they are causing the child and family. If possible meeting separately with the child after obtaining some information from the parents can be informative, as often the child's experience of symptoms may be different and may have preceded becoming outwardly noticeable to family

members and others. Holidays, birthdays, and other meaningful markers of time for children and families can be helpful in understanding onset and chronicity of symptoms. Possible questions include “Do you remember feeling this way last school year?” “What grade did you first notice...?”, and “Was it the same, better, or worse last summer?”. These anchors/markers can be useful in obtaining a timeline.

Confounders and Comorbidities

Depression can co-occur with other disorders, and healthcare professionals should seek accurate diagnosis and rule out diagnoses for other common childhood disorders characterized by troublesome behavior such as attention deficit hyperactivity disorder, oppositional defiant disorder, and anxiety and trauma-related disorders.

Medical conditions can mimic signs and symptoms of depression. Medical illness is also a risk factor for comorbid depression with medically ill children and adolescents having depression rates twice as high as the general population [24]. In the pediatric setting, it is important to distinguish between primary mood disorder, mood symptoms as a reaction to medical illness, and mood symptoms secondary to a primary medical condition [25]. This is sometimes difficult to determine. Specifically, in children, as mentioned earlier in the chapter, depression can be marked by symptoms of irritability and misbehavior or be associated with somatic complaints, causing the diagnosis to be misidentified. Common physical manifestations of depression in children include headaches, abdominal pain, joint pain, fatigue, and insomnia [24].

On the other end of the spectrum, there are several medical conditions that have been etiologically linked to depression. Common conditions include seizure disorders, post-concussive syndrome, cancer, sleep apnea, mononucleosis, anemia, failure to thrive, endocrine disorders, and other metabolic imbalances [24, 26]. These conditions often have overlapping symptomatology with depression, such as weight changes, sleep disturbance, and fatigue. When medically indicated, it is important to diagnose an underlying medical condition based on history and physical exam. Laboratory assessment of thyroid, hepatic, and renal function may be indicated, along with metabolic and hematologic status [24]. Some cases may warrant imaging and further diagnostic tests.

Recognition of comorbid depression is important for improvement in function and quality of life. Though most studies have been done in adult populations, it has been shown that depression is associated with engagement in health-risk behaviors, such as overeating, smoking, and sedentary lifestyle [27].

Research suggests that there is a mutually influential relationship between substance use and psychiatric comorbidities [28]. Alcohol, drug, and tobacco use can be a precipitant for depression or occur as a result of depression [3]. Moreover, substance use disorder and depression can share common risk factors such as family conflict and exposure to violence and other adversities in childhood [10, 29]. Some overlapping symptoms of depression and substance abuse include lack of interest,

fatigue, functional decline, sleep disturbance, and problems with concentration. These symptoms may be associated with intoxication or withdrawal. Withdrawal from nicotine can be associated with irritability, difficulty concentrating, and depressed mood [10]. The use of marijuana, particularly at high quantities, can be associated with low motivation. Opiate dependence is increasingly becoming a major health problem among teenagers, with opioid dependence leading to school failure, criminal activity, and even death due to overdose [29]. Cocaine initially causes euphoric effects but is associated with a post-intoxication blues, marked by irritability, fatigue, drowsiness, and depressed mood. One study showed effectiveness of fluoxetine in adolescents with comorbid substance use disorder and depression [30].

Screening and Measures

The American Academy of Pediatrics Bright Futures recommends psychosocial/behavioral assessment and screening at well-child visits. The US Preventive Services Task Force recommends depression screening for all teens ages 12–18. Recommended measures can be found in Table 10.2. While questionnaires and screeners can be used in the pediatric setting to obtain information about mood and depressive symptoms [44], a screener alone is not sufficient for diagnosis, and best practice includes proper attention to total scores, individual items, and information gathered directly from the child and family. Identifying a shared vocabulary during initial conversations about the child's depressive symptoms using the terminology that the child or family uses (e.g., sad, depressed, gloomy, stuck) is a patient-centered approach to mood assessment that attempts to match developmental and cultural considerations of the child and adolescent. Additionally, all children or adolescents discovered to have a depressive disorder should also be screened for trauma, anxiety, and substance use disorders.

Initial Management

Depression treatment starts with diagnosis and engagement of patients and families in understanding the diagnosis and treatment options. Treatment recommendations are made on the basis of symptom severity and impairment in function. If there is concern for acute safety and/or report of suicidal ideation, the patient should be referred for acute emergency psychiatric evaluation. For non-emergent cases, treatment can include behavioral interventions, psychotherapy, medication, or, more often, a combination of the three.

Depression is categorized by severity and course. Severity can be mild, moderate, or severe depending on the number and intensity of symptoms and degree of functional impairment [2]. For mild to moderate depression, behavioral interventions and psychotherapy alone can be an adequate treatment. Moderate to severe depression generally requires a combination of pharmacological and behavioral

Table 10.2 Clinical assessment tools for depression and mood symptoms

Measure	Domain	Age validated No. of items	Completed by	Administration and scoring times Training (none, unless otherwise indicated)	Languages available	Reference
Pediatric symptom checklist—35 (PSC)	Interpersonal domains, psychosocial dysfunction	4–16 years 35 items	Parent	<5 min Scoring 2 min	Translated in >20 languages ^a	Jellinek et al (1998) [31]
Patient Health Questionnaire-9-Modified for Teens (Modified-PHQ9)	Depressive symptoms based on DSM criteria	12+ years 9 items	Youth	5 min Scoring: 1–2 min	English and Spanish	Spitzer et al (1999) [32]
Patient Health Questionnaire-Adolescent (PHQ-A)	Includes question about self-harm/suicide					
Pediatric Symptom Checklist-17 (PSC-17)	Screeners for general emotional and behavioral problems Includes items relevant to mood	4–18 years 17 items	Parent	<5 min Scoring: 2 min	English, Spanish, Chinese, Vietnamese	Jellinek et al (1986) [33]
Revised Children's Anxiety and Depression Scale (RCADS)-Youth and Parent Versions	Anxiety, depression	8–18 years 47 items	Youth and/or parent	5–10 min Excel scoring sheets online available for English versions in children grade 3 and up at http://www.childfirst.ucla.edu/resources.html Hand scoring: 5 min	English, Spanish, Danish, Dutch, Korean	Chorpita et al (2005) [34]
Center for Epidemiological Studies Depression Scale for Children (CES-DC)	Depressive symptoms	14+ years 20 items	Youth	5 min Scoring: 2–3 min	English ^b	Radloff (1977) [35]

(continued)

Table 10.2 (continued)

Measure	Domain	Age validated No. of items	Completed by	Administration and scoring times Training (none, unless otherwise indicated)	Languages available	Reference
Mood and Feelings Questionnaire (MFQ)	Depressive symptoms	6–17 years 33 items	Youth and/or parent	5–10 min Scoring: 5 min	English	Angold et al. (1987) [36]
Short Mood and Feelings Questionnaire (MFQ-SF)	Depressive symptoms	6–17 years 13 items	Youth and/or parent	<5 min Scoring: 2–3 min	English	Angold et al. (1995) [37]

Psychometric references for the CESD: [34, 38–40]

Psychometric references for the PHQ9: [41–43]

^ahttp://www.massgeneral.org/psychiatry/services/psc_forms.aspx for complete list of languages

^bHas been translated into Arabic, Spanish, and Norwegian but less psychometric testing is available for those forms

interventions. In the primary care setting, this often warrants initiation of medication while awaiting engagement in additional services, including psychotherapy or child and adolescent psychiatry. In collaborative care models, depending on licensure, training, and state regulations, the behavioral care manager may be able to initiate psychotherapy.

Psychosocial and Behavioral Interventions

Psychoeducation involves sharing information about depressive symptoms, diagnostic procedures, and prognosis with children and caregivers. Psychoeducation can also be utilized as a collaborative method for establishing shared expectations with children and families. Psychoeducation as a stand-alone intervention shows mixed effectiveness in prevention and treatment of youth depressive disorders, but is an intervention that can be executed by many members of the primary care team.

Therapeutic interventions require specialized skills and training, and primary care providers (PCPs) are not expected to conduct psychotherapy with their patients. However, some awareness about the evidence base regarding a given disorder for the types of therapy offered by mental health clinicians in the community or co-located in primary care clinics can be useful for collaboration and informed decision-making about referrals. In addition, basic skills in evidence-based goal setting and behavioral techniques such as motivational interviewing, behavioral activation, pleasant activity scheduling, problem-solving, and generating alternative perspectives have been found to be effective interventions for depression [45–49]. PCPs can utilize elements of these interventions for initial management [50, 51]. In addition, skills in collaborating with children and families around treatment planning are crucial [52].

Cognitive behavioral therapy is effective for treating mild to moderate child and adolescent depressive symptoms [45, 53, 54]; however, there is variability in the long-term staying power of treatment [46, 53]. Interpersonal therapy has been found to be effective for mild to moderate depression in adolescents [46]. Targeted interventions for youth with depression or risk factors for depression have been shown to be more effective than universal prevention programs for youth depression [47, 48], suggesting the utility of appropriate depression screening and history gathering.

Mood tracking is a simple behavioral monitoring strategy and intervention that can be offered by pediatricians during initial management. This involves asking the child or adolescent to identify and track their mood for a specified time frame (usually 1–2 weeks). A mood diary, journal, pictures, or list can be used. Reviewing the diary while listening for patterns can provide information about duration, intensity, and malleability of mood (e.g., when, where, and in which situations mood is high or low), as well as identify opportunities for introducing more specific interventions (e.g., behavior activation, pleasant activities, problem-solving).

Behavior activation addresses symptoms of low mood, fatigue, and anhedonia that contribute to isolation and less participation in daily activities and routines. Behavior activation can include enjoyable activities such as going for a walk,

drawing a picture, calling a friend, or regular day-to-day activities such as folding laundry. Active participation (e.g., drawing a picture) is better than passive participation (e.g., watching TV); however, buy-in and motivation are also important; therefore soliciting a variety of activities to choose from (3–4) is often a useful start. The aim of behavior activation is to break the cycle of low mood and low activity. PCPs can help children and families develop daily routines and structure as an initial management strategy.

Pleasant activity scheduling helps youth with depression identify activities that are pleasant and enjoyable. The aim of pleasant activity scheduling is to reduce the cycle of inactivity, anhedonia, and negativity and consequently boost mood with active participation in activities.

Problem-solving encourages youth with depression to identify a target problem and brainstorm solutions. This active coping strategy is intended to help youth identify multiple possible solutions to a pressing concern or problem. By doing so, the goal is to reduce negative thinking and hopelessness and increase mastery and coping skills.

Relaxation and mindfulness skills can assist in coping with negative affect and somatic distress and distract from negative thoughts. Guided imagery, progressive muscle relaxation, and diaphragmatic breathing are examples of techniques that can be taught during initial management of emotional distress. Several online resources and YouTube videos are available that can aid the caregivers in initiating practice.

Encouraging parent/caregiver involvement is especially important for young children with depressive symptoms. Goals include increasing positive reinforcement and communication in the child's environment. Key points for parental and family education are listed in Table 10.3.

Mobile Applications and Technologies

There are free and low-cost child- and family-friendly apps for mood tracking (e.g., Mood Meter), relaxation (e.g., Breathe2Relax), and activities. Additionally, there are websites that help compare app cost and functionality (www.wellocracy.com). As new apps and technologies continue to emerge, it can be difficult to keep up; however, PCPs can offer guidance in selecting apps based on evidence-based strategies (e.g., mood tracking, behavior activation, relaxation) and encourage families to look for apps that augment these strategies while conveniently fitting with their routines [61, 62]; and to empower families to compare, try out, and report back their experience. A review of apps developed after 2007 found that the most common behavioral components in mobile apps included self-monitoring, feedback and action alerts, and social support [63].

Psychopharmacologic Interventions

For cases of depression with higher severity that require medication management, treatment can be divided into three phases: acute, continuation, and maintenance [4]. During the acute phase, treatment with an antidepressant is initiated and titrated

Table 10.3 Key points for parental/family education [19, 47, 52, 55–60]

Provide a description of depressive symptoms: It is important for families to know that a child with depression may not look sad and that depression may look like irritability and anger. It is also important for families to know that depression is not their fault.

Encourage families to remain active: Explain the cycle of doing less leading to feeling worse and the role of activities and routines (e.g., behavior activation). It is helpful for families to know how they can help by including pleasant routines and family time in their schedule as much as feasible.

Encourage families to plan ahead: Develop a coping plan for parent and child to include stress relief/self-soothing/relaxation activities, social supports, and who to talk to, what to do now, and what to do if symptoms worsen.

Identify family strengths and psychosocial supports: Explain the role of social support and capitalize on existing prosocial and supportive relationships among family members and peers.

Address emergency and safety planning: It is important for families to know that asking about suicide does not lead to suicide. Not asking is far more dangerous. Modeling ways to ask about how their child is feeling and providing safety planning supports (emergency/crisis numbers and procedures) can help caregivers feel more comfortable observing and asking their child about risk.

Address concerns about treatment: Although individual psychotherapy, family therapy, pharmacotherapy, or some combination may be warranted, families may experience worries and hesitation about beginning treatment. Worries may derive from stress and uncertainty, concerns about side effects, stigma, and/or cultural experience. Listen carefully to families' concerns, welcome questions, and provide information in a way that is open, accurate, and clear.

Identify potential risks in the home: Access to lethal means, especially guns, should be restricted or eliminated. Also, any old or surplus prescription or over-the-counter medications with abuse potential should be promptly and properly removed from the home.

to a response dose. In the continuation phase, treatment is continued for 6–12 months to achieve remission [4]. Lastly, the goal of the maintenance phase is to prevent recurrence by continuation of medication and/or booster therapy session. Maintenance phase is particularly important for children and adolescents who already experienced a prior depressive episode or suffer from more severe symptoms [4, 64].

Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of antidepressant treatment for children and adolescents. The response rate for SSRIs is 40–70%. However, placebo response rate is quite high; therefore, the calculated number needed to treat is 10 [4]. Fluoxetine, which was the first medication approved by the FDA for the treatment of depression in children and adolescents, has shown the largest difference between medication and placebo response. The second, and only other antidepressant approved by the FDA for the treatment of depression in children and adolescents, specifically ages 12 and up, was escitalopram [3]. Other SSRIs, including citalopram, sertraline, and paroxetine, have been shown to be effective in children and adolescents for other mental health conditions [3, 10]. Other antidepressants such as venlafaxine and bupropion have also demonstrated efficacy in the treatment of depression in adolescents [3–5, 10]. Tables 10.4 and 10.5 include medication charts for quick reference. Table 10.6 contains talking points for parents about the initiation of antidepressants.

Table 10.4 Antidepressant medications [3, 4, 10, 64]

Selective serotonin reuptake inhibitors (SSRI)				
Medication	Initial dose, mg	Target dose	Maximum dose, mg	Clinical considerations
Escitalopram (Lexapro)	5–10	Children 10–20 mg Adolescents 10–20 mg	30	FDA indication for treatment of depression in ages 12 and up; lower risk of drug-drug interactions, intermediate half-life Available in liquid formulation
Fluoxetine (Prozac)	10	Children 20 mg Adolescents 20–40 mg	60	FDA indication for treatment of depression in children and adolescents. Also approved for treatment of OCD in children 7 and up Long half-life; potential for drug-drug interactions Available in liquid formulation
Fluvoxamine (Luvox)	25	Children 50–200 mg Adolescents 50–200 mg	200 300	FDA indication for treatment of OCD in children 8 and up Drug-drug interactions due to inhibition of CYP1A2, CYP2C9, and CYP3A4
Sertraline (Zoloft)	12.5–25	Children 50–200 mg Adolescents 50–200 mg	200	FDA indication for treatment of OCD in children 6 and up Intermediate half-life Available in liquid formulation
Citalopram (Celexa)	10	Children 20–40 mg Adolescents 20–40 mg	60	Fewer drug interactions and fewer side effects Potential for QTc in combination with pimozide Available in liquid formulation
Paroxetine (Paxil)	10	Children 10–30 mg Adolescents 20–40 mg	50	No FDA indication for use in children or adolescents with depression; particular concern re: SI Short half-life; higher risk of discontinuation syndrome; requires a slower taper on discontinuation; slightly greater potential for wt gain Available in liquid formulation

With the initiation of any antidepressant medication, start low and increase slowly. Clinical response usually occurs in 4–6 weeks after medication is titrated to a treating dose [64]. In cases of moderate depression in which a trial of an antidepressant is warranted, treatment can be initiated and managed in the primary care setting. For children and adolescents, close monitoring for suicidal ideation, suicidal behaviors, and other side effects upon initiation of treatment is required. Monitoring is particularly important for children or adolescents with a history of

Table 10.5 Non-SSRI antidepressant medications for depression [3, 4, 10, 64]

Medication	Medication class	Initial dose	Target dose	Maximum dose, mg	Clinical considerations
Bupropion (Wellbutrin) Bupropion SR	NDRI	100 mg	Children 150–300 mg Adolescents 300 mg	300	Contraindicated with arrhythmias, atrioventricular block, bulimia, and seizure history; lower rate of sedation; weight neutral
Bupropion XL	NDRI	150 mg	Children 150–300 mg Adolescents 450 mg	450	Slightly lower risk of seizure; otherwise, same as above
Desvenlafaxine (Pristiq)	SNRI	50 mg	Children 50 mg Adolescents 50–100 mg	100	Requires gradual taper for discontinuation, risk of excessive sweating, palpitations, and tachycardia
Duloxetine (Cymbalta)	SSNRI	20 mg twice a day	Children 40–60 mg Adolescents 40–60 mg	60	Also indicated for chronic pain and urinary continence; risk of elevated blood pressure; potential for drug-drug interaction via inhibition of CYP2D6; avoid use in hepatic disease
Mirtazapine (Remeron)	NaSSA	7.5– 15 mg	Children 15–45 mg Adolescents 15–45 mg	45	Useful for insomnia due to sedative effects; associated with weight gain and increase in appetite; rare risk of neutropenia Available in dissolvable formulation
Trazodone (Desyrel)	SARI	25– 50 mg	Children 100–150 mg Adolescents 100–150 mg	150	Sedative effects; can cause postural hypotension; rare risk of priapism; not commonly used as a monotherapy
Venlafaxine XR (Effexor)	SSNRI	37.5 mg	Children 150–225 mg Adolescents 150–225 mg	300	Acts as an SSRI at low dose; also indicated for chronic pain; use with caution with hepatic impairment Can cause excessive sweating and tachycardia

NaSSA noradrenergic and specific serotonergic antidepressant, *NDRI* norepinephrine-dopamine reuptake inhibitor, *SARI* serotonin agonist and serotonin reuptake inhibitor, *SSNRI* selective serotonin-norepinephrine reuptake inhibitor

self-injurious behavior, impulsivity, or family history of bipolar disorder [3]. While this text will include the most common and/or concerning potential side effects, the FDA package insert for each medication will include a comprehensive list of adverse effects.

Common side effects of SSRIs, reported by 10–20% of those prescribed, in the initiation of treatment include drowsiness, weight gain, insomnia, dizziness, anxiety, headache, and sexual dysfunction [10, 64]. Particularly in younger children, SSRIs may be associated with disinhibition, agitation, and anxiety. Other side effects to consider when prescribing an SSRI are nausea, rash, daytime malaise, and cognitive dulling [10]. These side effects are typically short-lived or tolerable, but reducing the dose, if recently increased, or dividing the dose may be helpful. If intolerable side effects persist, management with adjunct medication or switching to another antidepressant may be required. There is a risk of mania in children and adolescents with genetic vulnerability; therefore, assessment of family history for other mood or psychotic disorders is essential [4]. Other possible serious adverse reactions, which are rare, include excessive bruising, prolonged bleeding time, hyponatremia, serotonin syndrome, and extrapyramidal symptoms [64]. The risk of these reactions is increased with children with other medical problems requiring management with multiple medications or other medical interventions. Antidepressants should not be discontinued abruptly as it can result in discontinuation syndrome, which can include agitation, sleep disturbance, paresthesia, and dizziness.

Black Box Warning for Suicidal Ideation in Youth on Antidepressants

In 2004, the FDA issued a black box warning on antidepressants due to an associated increase in suicidal ideation and behavior. The rate of the increase was 4% compared to 2% in patients receiving placebo when randomized clinical trials were analyzed in a series of meta-analyses. There were no completed suicides in the pooled trials [67]. The black box warning has been controversial as it has been associated with a decrease in antidepressant prescribing, particularly in the primary care setting, and a decrease in new diagnoses of depression [68]. However, the suicide rate has continued to rise steadily. More recent data show that the rate of use has returned to the rate prior to the warning [69]. Given the known association between suicide and severe depressive symptoms and the improvement of suicidal ideation with continued treatment with SSRI, the use of antidepressants when indicated outweighs the risk of increase in suicidal ideation with the initiation of treatment [4]. However, close monitoring and assessment of suicidal ideation is warranted whenever a child or adolescent is diagnosed with depression and started on an antidepressant. Of note, multiple studies indicate that paroxetine (Paxil) is of particular concern [70, 71].

Table 10.6 Talking points for parents about initiation of antidepressants [65, 66]

Review indication for treatment: Depression is an illness that has physical, cognitive, and behavioral effects. If depression is not treated, it can last close to a year or longer and impairs functioning at school and home. Depression also increases risk for suicide and other behavioral problems.

About 60% of children/adolescents will improve with treatment with an antidepressant. Even more children/adolescents respond with medication and therapy.

Discuss treatment options: There are two medications approved by the FDA for treatment of depression in children and adolescents. There are other antidepressants with studies to support their use that are also commonly used to treat depression in children/adolescents. The combination of medication and therapy is the most effective treatment for moderate and severe depression.

Discuss treatment course: It can take 4–6 weeks for your child to respond to antidepressant treatment once medication is increased to a treating dose. During that time, we will monitor symptoms and increase dose as needed. It is also recommended that you help your child continue healthy habits with a regular sleep schedule, regular exercise, and a well-balanced diet.

Discuss potential side effects: Antidepressants (SSRIs) are generally well tolerated. Side effects are reported by less than 20% of patients. The more common among side effects reported are stomach upset, weight gain, headache, and sleep changes. Parents should be attentive to signs of increased anxiety, irritability, aggressiveness, or impulsivity. In a small number of instances, a child or adolescent might have extreme reactions to antidepressants as a result of genetic, allergic, drug interactions or other unknown factors.

Discuss suicide risk: In 2004, the FDA issued a warning (black box warning) after reviewing 23 studies of nine antidepressants. They found an elevated risk of suicidal ideation and behavior among those taking antidepressants. A later study showed an elevated but smaller risk. No suicides occurred in any of these studies.

Research suggests that any increased risk of suicidal thoughts or behaviors is most likely to occur during the first 3 months of treatment, with some studies showing that the risk is highest in the first 3–6 weeks.

Through careful monitoring, safety planning, and the combination of medication with psychotherapy, the risks for increased suicidal thoughts can be managed. *In the vast majority of cases of moderate to severe depression, the risk of SI posed by untreated depression is of greater clinical significance than the risk of SI associated with antidepressant medication.*

Address emergency and safety planning: The provider will work with you (the family), your mental health clinicians, and your other providers to develop an emergency action plan, called a “safety plan,” that is, a planned set of actions for family and physician to take if and when your child has increased suicidal thinking.

- A safety plan can be a simple agreed-upon understanding between physician and family in which the family is provided with a 24-h number available to deal with crises (number for on-call physician, mobile crisis team, or 911). Physician should discuss minimizing access to potentially harmful items in the home: lethal means of suicide, such as guns or large quantities of dangerous medications, including over-the-counter drugs, should be removed from the house or stored in an inaccessible location.
 - In the case of a crisis, it must be emphasized that antidepressants should not be discontinued abruptly as it can result in discontinuation syndrome which can include agitation, sleep disturbance, paresthesia, and dizziness.
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When to Refer

In cases of mild depression, psychotherapy is the first line of treatment. If significant stressors are present, psychotherapy and/or social service resources should also be considered. If symptoms are present in children under 6, referral for a comprehensive diagnostic behavioral health evaluation is recommended as more intensive parent guidance and family-focused intervention are likely warranted. If a patient has severe side effects from SSRI, does not improve with a second trial of an SSRI, or has complex psychiatric comorbidities, referral for psychiatric evaluation to clarify any diagnostic questions or further augment treatment may be necessary. Due to limited access to mental health providers, in cases with higher severity or complexity, referrals for specialized services should be made early as there may be a wait for enrollment in treatment, while symptoms are managed in the primary care setting.

Key Considerations for Follow-Up

Follow-up visits can be used to safely titrate the antidepressant to a therapeutic dose. It is important to note that many patients, about 60%, may have a partial or no response to their first trial of antidepressant. Common reasons for lack of response are inadequate dosing, inadequate duration, and intolerable side effects [64]. Initial titration for children should be a slow process, increasing by incremental doses every 1–2 weeks. Titration may be limited by side effects. An adequate trial is defined as 6 weeks at a treating dose; however, most patients have at least a partial response to an adequate dose in the first 2–4 weeks. If symptoms persist within therapeutic dose range, continue titration. Maximum dose for an individual patient is determined by response or therapeutic safety parameters. If symptoms have not remitted after 12 weeks at a tolerated maximum therapeutic dose, consider switching to another SSRI or atypical antidepressant. If side effects are intolerable or there is no response with the first trial of an SSRI, a trial of a second SSRI or SNRI is needed. Half-lives of sertraline, citalopram, paroxetine, and sustained-release bupropion are shorter in children than reported in adults, so they may be at greater risk for discontinuation syndrome or require more frequent doses of some medications to maintain steady state [72, 73]. Once a child or adolescent is having no or minimal depressive symptoms, the same treatment should be continued for at least 1 year. If there is a history of prior depressive episodes or the current episode is chronic and/or severe, it is recommended that treatment is continued for a longer period of time [3].

The decision to discontinue antidepressant treatment after sustained remission should be discussed with family and mental health providers. As the therapist is often the mental health specialist with the most frequent contact with the patient, their input can be very helpful. While most children and adolescents recover, an episode of major depression recurrence is common. Recurrence occurs in about 40% of children and adolescents over a 5-year period [46]. In the case of a

recurrence, reinitiating previously effective antidepressant treatment is recommended, though the response may vary from episode to episode.

In some cases of moderate to severe depression, depressive symptoms may interfere with a child's ability to fully participate in psychotherapy without a trial of an antidepressant first. In these cases, following the guidelines above, as well as obtaining permission to communicate with the child's mental health providers, is important for coordinated treatment decisions. Follow-up visits should also include asking the family and child directly about psychotherapeutic treatment progress. A meta-analysis conducted by Weisz and colleagues [46] found variability in long-term effects of psychotherapy for depressed adolescents beyond 1-year follow-up, suggesting periodic follow-up and assessment after treatment ends may be warranted.

Conclusion

Depression in children and adolescents often first presents in the primary care setting. Recognizing the symptoms early can lead to early interventions and decrease distress and impairment of function. Symptoms of depression can alter a child's cognitive, behavioral, and physical state. In assessing children and adolescents, it is important to engage the family in determining level of impairment and making a treatment plan. Treatment is likely to start in the primary care setting while the family is referred for specialized mental health treatment. This may include simple behavioral interventions and treatment with antidepressant medication as indicated. Antidepressant treatment has been shown to be effective in children and adolescents. Though generally well tolerated, parents and providers need to monitor for side effects. A safety plan should be established with the parents of all children and adolescents with depression.

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