Recognizing and treating depression in children and adolescents

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Purpose. The clinical presentation and neurobiology of depression in youth and its appropriate treatment, as well as strategies for improving therapeutic benefit and preventing adverse outcomes, including suicide, are reviewed.

Summary. Functionally impairing depression occurs in 2–10% of children and adolescents. A diagnosis of depression should be considered when a physically healthy child exhibits depressed mood or anhedonia, multiple somatic complaints, or behavioral changes, such as bullying, aggression, and social withdrawal. Risk factors for depression include childhood trauma, genetic susceptibility, and environmental stressors. Antidepressants and cognitive behavioral therapy are the most effective treatments for adolescents with depression. Youth are at risk for the same adverse effects as adults but have an increased risk of behavioral activation, or switch, to mania and suicidal thoughts and behaviors early in treatment. Compared with other antidepressants, fluoxetine has the most evidence for safety and efficacy, particularly in adolescents 12 years or older. There is very little evidence for the effectiveness of any antidepressant in children 11 years and younger. Youth receiving antidepressants should be monitored closely for new-onset or worsening suicidality, particularly during the first two weeks after starting medication, and for three months of therapy. Behavioral activation, aggression, worsening depression, anxiety, insomnia, or impulsivity can herald a switch to mania or suicidality.

Conclusion. Depression in youth is common and treatable and responds best to multimodal treatment combining patient and family education, cognitive behavioral therapy, and antidepressant medication. The potential benefits of antidepressants outweigh the risks for adolescents. Family and psychotherapeutic interventions are most effective for prepubertal children.

Index terms: Adolescents; Antidepressants; Cognitive therapy; Depression; Diagnosis; Fluoxetine; Patient information; Pediatrics; Suicides; Toxicity

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In March 2004, the Food and Drug Administration (FDA) issued a public health advisory cautioning physicians, their patients, and their patients’ families to closely monitor both adults and children with depression for the emergence of suicidal behavior after beginning antidepressant therapy. In October 2004, FDA required manufacturers of antidepressants to add a black-box warning to the labeling of antidepressants regarding an increased risk for new-onset suicidal behavior in children and adolescents taking antidepressants. This advisory was based on the results of 24 placebo-controlled trials of 4400 children and adolescents, which found that antidepressant use was associated with an approximate 4% frequency of new-onset suicidal behavior compared with a rate of approximately 2% with placebo. None of the children in the clinical trials completed suicide. The FDA advisory committee recommended that antidepressants not be contraindicated in children and adolescents because access to them is necessary for those who benefit from the drugs.

The use of antidepressants in youth has received greater scrutiny since FDA issued that warning. Prescriptions written for antidepressants for children age 10–18 years decreased by 10–16% in 2004, compared with a 50% increase between 1998 and 2002. An increased awareness of teen suicide and the need for parent and family education about treatment options for depression have resulted from FDA’s warning. However, clinicians express concern that the black-box warning on antidepressant labeling will lead to increased rates of youth suicide due to decreased use of antidepressants to effectively manage depression. Strong support for the effectiveness of fluoxetine in treating adolescent depression exists in the literature. Cognitive behavioral therapy (CBT) also has proven efficacy for the treatment of depression in children and adolescents.
Although effective treatments for depression in youth are well established, community care for depression in children and adolescents is lacking, with serious gaps in access to care and a lack of ongoing treatment.10,11 This article reviews the clinical presentation of depression in youth, neurobiological and environmental risk factors associated with depression in youth, pharmacologic and nonpharmacologic treatment options, and recommendations for clinical monitoring and patient and family education.

Epidemiology and clinical course

An increasing body of knowledge confirms that depression is a common and persistent illness in youth, affecting 0.3% of preschoolers, 2% of elementary school-age children, and 5–10% of adolescents.12,13 The rates of prepubertal depression are similar for boys and girls; however, depression rates double in females after puberty.12,13 Hormonal and environmental influences are thought to contribute to the increased frequency of depression in female adolescents.14 Rates of depression increase dramatically as children move into adolescence.14 Comorbidities such as substance abuse and anxiety disorders increase the risk of depression by two- to threefold.15,14 An estimated 10–20% of adolescents have had at least one major depressive episode by age 18 years.15,14 One study of 9863 students age 10–16 years found that 29% of American Indian youth exhibited symptoms of depression, compared with 22% of Hispanic, 18% of Caucasian, 17% of Asian-American, and 15% of African-American youth.14

Untreated, a depressive episode can last seven to nine months, and approximately 50% of patients will relapse within five years of their first episode.12,15 Depression compromises the developmental process, with associated difficulties with concentration and motivation,15 leading to poor academic performance, impaired social functioning, poor self-esteem, and a higher risk of suicide.12,13,14

Clinical presentation. Major depressive disorder has been validated in children as young as 3 years (Table 1).16-18 For example, preschoolers may persistently show suicidal or self-destructive themes in play, or parents and caregivers may notice that a physically healthy child is uninterested in play.16 Depression in children 8 years or younger may not be recognized because this age group is less likely to verbalize the emotional symptoms of depression and more likely to display symptoms of anxiety (e.g., phobias, separation anxiety), somatic complaints (e.g., “my tummy hurts,” “I don’t feel good”), and auditory hallucinations.17,18 Depressed children are irritable, have temper tantrums, and display other problem behavior (e.g., shouting, lack of interest in playing with friends).18 Older children (age 9–12 years) talk about running away from home; display boredom, low self-esteem, guilt, or hopelessness; and have a fear of death. Compared with adolescents with depression, children with depression are less likely to suffer from delusions or make serious attempts to commit suicide.18

Depressed adolescents (age 12–17 years) display more sleep and appetite disturbances and are prone to reckless behavior, delusions, suicidal ideation and acts, and impairment of overall functioning.18 Depressed teenagers have more behavior disturbances and fewer neurovegetative symptoms (e.g., low energy, psychomotor slowing) than do adults with depression.12,18

When a child or adolescent displays new-onset depressive symptoms with or without psychosis, bipolar disorder should be seriously considered as a possible diagnosis.19,20 Risk factors for bipolar disorder include a family history of the illness, a history of antidepressant-induced mania, and

Table 1. Comparison of Clinical Presentation of Major Depressive Illness by Age8,12,16-18

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Frequency (%)</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥19</td>
<td>17</td>
<td>Depressed mood or anhedonia and at least four of the nine following symptoms that last at least 2 wk with functional impairment: (1) sleep and appetite changes, (2) psychomotor changes (slowing or agitation), (3) hopelessness, (4) worthlessness, (5) diminished energy, (6) poor concentration, (7) tearfulness, (8) suicidal thoughts, and (9) suicide plan</td>
</tr>
<tr>
<td>12–18</td>
<td>5–10</td>
<td>Same as adult criteria except more impulsivity, irritability, and behavioral changes; more reckless behavior; poor school performance; more sleep and appetite disturbances than displayed by younger children; suicidal thoughts and attempts similar to those in adults; genetic link to depression stronger; chronic course more likely</td>
</tr>
<tr>
<td>9–12</td>
<td>3–5</td>
<td>Same as adult criteria except more complaints of boredom, low self-esteem, guilt, hopelessness, wanting to run away from home, and fear of death</td>
</tr>
<tr>
<td>6–8</td>
<td>2–4</td>
<td>Same as adult criteria except for difficulty verbalizing feelings; more somatic complaints (e.g., “my tummy hurts,” “I don’t feel good”); outbursts of crying, shouting; unexplained irritability; anhedonia observed by others</td>
</tr>
<tr>
<td>3–5</td>
<td>0.3–0.5</td>
<td>Same as 6–8 yr olds, except symptoms not necessarily present over an entire 2-wk period; markedly diminished interest in play; feelings of worthlessness or suicidal, self-destructive themes persistently evident in play</td>
</tr>
</tbody>
</table>
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Psychomotor retardation associated with the depressive symptoms.\(^{19,20}\) It is important to screen for bipolar disorder in these patients because treatment with antidepressants is more likely to trigger mania in these individuals, thereby increasing the number or severity of suicidal behaviors.\(^{20,22}\) If a diagnosis of bipolar disorder is confirmed, a mood stabilizer (e.g., lithium, valproate) should be initiated before adding an antidepressant to treat persistent depressive symptoms.\(^{22}\)

Regardless of the presence of bipolar disorder, children and adolescents have a greater risk of developing antidepressant-induced manic conversion compared with adults.\(^{21,22}\) A longitudinal study of 87,920 patients taking antidepressants for any reason found that 4,786 patients (5.4%) age 5–29 years developed manic conversion.\(^{21}\) Prepubertal or peripubertal children age 10–14 years had twice the risk of manic conversion, approximately 10%.\(^{21}\) In pediatric psychiatry clinics in the late 1980s and early 1990s, the rate of antidepressant-induced behavioral activation, hypomania, or mania was approximately 20–50%.\(^{23}\) The higher rate was likely due to the inclusion of youth with bipolar disorder and the relatively higher starting dosages of antidepressants in older clinical trials.\(^{22,23}\)

**Comorbidities.** A depressed youth with no other psychiatric diagnosis is a rarity. Common comorbid conditions include attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), substance abuse, posttraumatic stress disorder (PTSD), dissociative states, and trauma-related hallucinations.\(^{12}\) The presence of multiple comorbid conditions and psychosocial stressors increases the severity and chronicity of the depressive episode.\(^{12,14}\)

In addition, combinations of medications can increase the risk of adverse drug reactions and drug interactions.\(^{23,24}\) An evaluation of treatments for depression in the community found that 44% of children prescribed antidepressants were taking a concomitant psychotropic medication.\(^{10}\)

**Etiology and risk factors**

Youth involved in behaviors such as bullying and substance abuse and those with frequent somatic complaints have higher rates of depressive symptoms compared with those not exhibiting such behaviors.\(^{14}\) High familial loading for a mood disorder (i.e., at least one first-degree and at least one second-degree relative has a mood disorder), a mother’s lifetime anxiety disorder, and a behavioral disorder in the child increases the risk of developing a depressive disorder by threefold.\(^{25}\) Other risk factors for developing depression include genetic predisposition and psychosocial stressors, such as maternal mental illness, lack of paternal communication, unsafe living conditions, physical or sexual abuse, and parental loss through death or divorce.\(^{12,14}\)

A longitudinal study conducted in New Zealand followed 1265 children from birth to age 21 and monitored factors associated with increased rates of depression and suicidal behavior.\(^{26}\) As expected, those exposed to sexual abuse, physical abuse, interparental violence, parental criminality, and parental use of illicit drugs had higher rates of depression and suicidal thoughts and behavior.\(^{26}\) Factors associated with resiliency to depression and suicidal behaviors were intact family support systems, positive peer affiliations, and high self-esteem.\(^{26}\)

**Neurobiology of depression.** Magnetic resonance imaging studies have shown measurable brain changes in children and adolescents with depression compared with nondepressed control subjects. The left subgenual prefrontal cortex volume was reduced in young women with adolescent-onset major depression compared with healthy controls.\(^{27}\) Anterior cingulate cortex glutamatergic concentrations were significantly lower in children with depression compared with age-matched controls.\(^{28}\) Blunted growth-hormone secretion is associated with an increased risk of depression in youth.\(^{29}\)

Smaller hippocampal volume was found in depressed women with a history of severe and prolonged abuse in childhood but not in depressed women who had not experienced similar abuse.\(^{30}\) Another study found smaller amygdala volumes in 20 children and adolescents with major depression compared with 24 healthy controls; hippocampus volumes did not differ between groups.\(^{31}\) There is increasing evidence of a link among early childhood trauma, depressive illness, and morphological brain changes, further substantiating the biological basis of depression in youth.\(^{28,30}\)

Neurogenetic studies provide additional evidence for the biological basis of depression. Caspi et al.\(^{32}\) found that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene moderates the influence of stressful life events on the development of depression. They assessed 1037 children (52% male) for depression and life stressors at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years. These children were divided into three groups on the basis of their serotonin-linked promoter region (5-HTTLPR) genotype: those with two copies of the S allele (S homozygotes) \((n = 147)\), those with one copy of the S allele (S/L heterozygotes) \((n = 435)\), and those with two copies of the L allele (L/L homozygotes) \((n = 265)\). The impact of life events on the self-reports of depressive symptoms was significantly stronger among individuals carrying an S allele than among L/L homozygotes \((p = 0.02)\).\(^{32}\)

Further analysis showed that stressful life events predicted suicidal ideation or attempt among individuals carrying an S allele but not among.
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L/L homozygotes. A separate case-control and family-based study lends support to these earlier findings. Sixty-eight depressed children and 68 age-matched controls found an excess of the S/S genotype (p = 0.025) and of the S allele (p = 0.021) among the children with depressive illness. It seems that depressed and suicidal children are more likely to receive the S allele of the 5-HTTLPR, and this may predispose them to developing depression in association with stressful life events. Polymorphisms in the 5-HTT protein can affect the use of serotonin by the neuron. Serotonin dysregulation is implicated in the pathophysiology of depression in youth, and most effective antidepressants modulate serotonin neurotransmission.

Suicidality. Suicidal thinking and attempts are common in youth with or without depression, with 19% of 15–19-year-olds thinking about suicide and 9% attempting suicide each year. If depressed, 35–50% will attempt suicide, and 2–8% will complete suicide over a decade. Longitudinal studies have found that increased rates of suicidal behaviors in youth are associated with a family history of suicide, childhood sexual abuse, personality factors (e.g., high rates of anxiety and novelty seeking), negative peer affiliations, lack of school success, and untreated behavioral disorders and depression.

Increased suicidality may also be related to developmental factors, such as the lack of coping mechanisms or “black-and-white” thinking, where youth see themselves and their life as “all good” or “all bad.” When things seem “all bad,” youth turn to suicide because they are unable to conceptualize other options to end their emotional suffering. Cognitive restructuring and behavioral interventions toward the development of coping skills and alternatives to suicide are two goals of CBT. CBT is considered a first-line treatment for depression in nonpsychotic youth.

Completed suicide in youth is considered rare, with an overall 12-month incidence of 0.008% in youth age 15–19 years. Suicide completion rates in youth actually decreased from 1995 to 2005. Reasons cited for this reduction include decreased access to firearms and increased recognition and treatment of depression. One study examined regional antidepressant use and national suicide mortality files of children and adolescents in 1990 and compared them with similar data collected in 2000. The study showed that for every 1% increase in selective serotonin-reuptake inhibitor (SSRI) use in 10–19-year-olds, there was a decrease of 0.23 completed suicide per 100,000 youth. This study of real-world antidepressant use in youth showed that antidepressants offer a protective effect against suicide completion. This finding conflicts with placebo-controlled clinical trials studying antidepressants in youth, which found increased suicidality early in treatment.

Another study analyzed the relationship between antidepressant pharmacy prescription volumes and U.S. suicide rates in all age groups between 1996 and 1998. The annual suicide rate in those three years was 12.32 suicides per 100,000 people. Investigators found that prescriptions for SSRIs and other new-generation antidepressants (nefazodone, mirtazapine, bupropion, and venlafaxine) were associated with a 33% lower suicide rate, or 8.2 suicides per 100,000 people, versus those not receiving antidepressants and those prescribed tricyclic antidepressants. A high number of prescriptions for tricyclic antidepressants in a county was associated with increased suicide rates, although counties with high rates of tricyclic antidepressant prescribing had fewer antidepressant prescriptions. These findings were consistent in children, adults, and the elderly. Similar to previous studies’ findings on risk factors of suicide completion, male sex was associated with higher suicide completion rates. Black females were the least likely to complete suicide.

In the United States, females receive more prescriptions for antidepressants compared with males, but males have significantly higher suicide completion rates. This sex difference applies to all ages, including children. According to several studies, most suicides and serious nonfatal suicide attempts are committed by individuals with major depression that was untreated at the time of death.

Treatment

Effective, first-line treatment options for depression in youth include CBT, interpersonal psychotherapy, antidepressants, psychosocial intervention, or a combination of non-drug and pharmacologic options.

In preschoolers and children under eight years of age, therapeutic interventions are primarily psychosocial, beginning with family counseling and environmental modifications. Psychosocial interventions are particularly helpful in very young children when it is clear that depressive symptoms are a reaction to a child’s environment. Examples of useful psychosocial interventions include treatment and support for depressed or overwhelmed parents. Antidepressants, CBT, and interpersonal psychotherapy have not demonstrated effectiveness in preschoolers or children under eight years of age.

Older children and adolescents have a wider range of effective treatment options, including CBT and antidepressants. The effectiveness of CBT versus antidepressants has not been adequately assessed in children and adolescents, although one study compared placebo with fluoxetine and CBT, fluoxetine alone, and CBT alone in depressed adolescents. Combination CBT and fluoxetine
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produced the best therapeutic outcome, and all treatments were more effective compared to placebo.

**Nonpharmacologic interventions.** CBT is considered the first-line treatment for children and adolescents with depression, with efficacy rates of 60–70%.

CBT is superior to interpersonal psychotherapy and other non specific psychotherapeutic interventions, such as supportive, psychodynamic, and family therapy, in relieving symptoms of nonpsychotic major depression.

CBT teaches patients to identify and counteract distortions in the way they view themselves and their circumstances.

Interpersonal psychotherapy focuses on problem areas of grief, interpersonal roles, transitions, and disputes. Interpersonal psychotherapy may be as effective as antidepressants for the treatment of mild to moderate depression in youth.

One study found that younger children and adolescents (10–14 years old) with less severe depressive symptoms and less psychosocial impairment may be more responsive to psychotherapeutic interventions compared with older adolescents with more severe symptomatology.

Another study showed that adolescents age 13–17 years with major depression and conduct disorder responded to CBT.

Most studies of CBT have been conducted with children age 9 years or older, as younger children may not have the verbal and cognitive processing skills to benefit from CBT.

**SSRIs.** A summary of published controlled trials of SSRIs for the treatment of major depression in youth is provided in Table 2. The place in therapy, initial pediatric dosages, and special considerations for using antidepressants with the most well-established efficacy in the treatment of major depressive disorder in youth are summarized in Table 3.

**Fluoxetine.** Fluoxetine is the only antidepressant with FDA-approved labeling for the treatment of depression in children age 8 years or older. The approval was based on two placebo-controlled trials. The first study found that fluoxetine 10–40 mg daily had significantly greater efficacy (56%) than placebo (33%) in children age 8–18 years for eight to nine weeks ($p = 0.02$). In the second study, the efficacy rates were 41% for children receiving fluoxetine and 20% for those receiving placebo ($p < 0.01$). These studies included children with comorbid ADHD, ODD, and bipolar II disorder. They did not stratify results by patient age. Headache was the only nonsolicited adverse event reported significantly more often in fluoxetine-treated patients versus those receiving placebo.

In the Treatment of Adolescents with Depression Study (TADS), 439 adolescents age 12–17 years were divided into four treatment groups: CBT, fluoxetine, CBT plus fluoxetine, and placebo. After 12 weeks of treatment, combination CBT and fluoxetine was superior to placebo on the Children’s Depression Rating Scale (CDRS)–revised ($p = 0.001$). Fluoxetine plus CBT was superior to fluoxetine alone ($p = 0.02$) and CBT alone ($p = 0.01$). Statistical analysis revealed that patients’ response to fluoxetine alone did not differ significantly from CBT plus fluoxetine, although both were superior to CBT and placebo.

Fluoxetine 10–40 mg/day was administered, with doses adjusted by a blinded clinician based on response during six follow-up visits over 6 weeks. The mean highest dosage of fluoxetine in each group ranged from 28.4 mg daily in the CBT plus fluoxetine group to 34.1 mg daily in the placebo group. Fifteen sessions of CBT were administered over 12 weeks. Adverse events were considered mild, with 10% of patients in all treatment groups except CBT alone reporting headache. Insomnia occurred in five CBT plus fluoxetine-treated patients, three patients receiving fluoxetine alone, and one patient in the placebo group. Upper abdominal pain was reported in six patients receiving fluoxetine alone and two in the placebo group. One patient receiving CBT plus fluoxetine and two patients receiving fluoxetine alone experienced irritability and hypomania.

### Published Trials of SSRIs Versus Placebo for the Treatment of Major Depression in Youth

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration (wk)</th>
<th>Age (yr)</th>
<th>No. Pts. (Drug/Placebo)</th>
<th>% Pts. Improved or Points on CDRS (Drug vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>8</td>
<td>8–18</td>
<td>48/48</td>
<td>–16.2 vs. –6.7 ($p = 0.002$), 56 vs. 33 ($p = 0.02$)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>8</td>
<td>8–17</td>
<td>209/210</td>
<td>65 vs. 53 ($p = 0.03$)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>10</td>
<td>6–11</td>
<td>86/91</td>
<td>–24 vs. –22 (NS)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>8</td>
<td>12–18</td>
<td>93/87</td>
<td>–21.5 vs. –18.2 ($p = 0.01$), 65 vs. 48 (NS)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>8</td>
<td>12–18</td>
<td>95/87</td>
<td>69 vs. 59 (NS), 52 vs. 48 (NS)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>8</td>
<td>7–17</td>
<td>89/85</td>
<td>36 vs. 24 ($p &lt; 0.05$), 47 vs. 45 (NS)</td>
</tr>
</tbody>
</table>

aSSRIs = selective serotonin-reuptake inhibitors, CDRS = Children’s Depression Rating Scale, CGI = Clinical Global Impressions, NS = not significant, HAMD = Hamilton Depression Rating Scale.
Suicidal thoughts occurred in 29% of all TADS participants at baseline but improved in all treatment groups. Patients receiving fluoxetine plus CBT demonstrated the greatest decrease in suicidal thinking \((p = 0.02)\). Seven patients (1.6%) attempted suicide (four CBT plus fluoxetine treated, two fluoxetine treated, one CBT treated, and zero in the placebo group), with no completed suicides. Patients with known risk factors for suicide completion (bipolar disorder, history of substance abuse, psychotic illness, or a suicide attempt within the past six months) were excluded from the study. The results of TADS are generalizable to adolescents treated in the community. Half of patients enrolled in TADS had at least one comorbid diagnosis, and their mean illness severity ranged from moderate to moderately severe as measured on the CDRS. However, the results lacked generalizability to those with multiple episodes of depression; 86% of study participants were experiencing their first episode of depression. Because patients’ mean age was 14.6 years, results cannot be generalized to children under 12 years of age.

_Sertraline._ Before FDA issued warnings about increased suicidality associated with SSRIs, sertraline was the most commonly prescribed antidepressant in youth. In 2002, 10.8 million prescriptions for sertraline were dispensed to children and teens (0–17 years) of all TADS participants at baseline. Half of patients enrolled in TADS had at least one comorbid diagnosis, and their mean illness severity ranged from moderate to moderately severe as measured on the CDRS. However, the results lacked generalizability to those with multiple episodes of depression; 86% of study participants were experiencing their first episode of depression. Because patients’ mean age was 14.6 years, results cannot be generalized to children under 12 years of age.

Sertraline’s FDA-approved labeling for the treatment of obsessive-compulsive disorder (OCD) in children age six years or older, coupled with the drug’s lower risk of drug interactions compared with fluoxetine and fluvoxamine, likely contributed to the higher prescribing rate for sertraline relative to other SSRIs.

The evidence for sertraline’s effectiveness in treating depression in youth is not robust. Pooled data from two studies comparing sertraline 50–200 mg daily for 10 weeks versus placebo in depressed children and teens show a 69% response rate for sertraline versus 59% for those receiving placebo. After further examination of the individual patient groups, patients age 6–11 years receiving sertraline \((n = 86)\) did not differ from those receiving placebo \((n = 91)\) in their clinical outcome. Adolescents age 12–17 years \((n = 103)\) demonstrated a significant improvement in depressive symptoms versus the placebo group \((n = 96)\), as measured by the CDRS \((p = 0.01)\). Adverse effects from sertraline treatment that were more frequent than with placebo were insomnia, anorexia, diarrhea, vomiting, agitation, and urinary incontinence, the last of which was more frequent in children age 11 years or younger. Suicide was attempted by two patients in the sertraline group and two in the placebo group.

_Paroxetine._ Paroxetine was the second most commonly prescribed SSRI in 2002, despite only one published trial describing its efficacy on the secondary outcome measure, the Clinical Global Impressions (CGI) scale. There was no difference between paroxetine and placebo in the improvement of depression on the primary outcome measure, the Hamilton Depression Rating Scale (HAM-D). This eight-week trial compared the effect of paroxetine \((n = 93)\) to imipramine \((n = 87)\) and placebo \((n = 95)\) in adolescents age 12–18 years. Exclusion criteria included the presence of bipolar illness, schizoaffective disorder, alcohol or substance use, PTSD, and current suicidal ideation or plans.

Ten patients treated with paroxetine developed adverse psychiatric events, including worsening depression \((n = 2)\), emotional lability with

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**Table 3. Antidepressants with Well-Established Efficacy for the Treatment of Major Depressive Disorder in Youth**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Place in Therapy</th>
<th>Initial Dosage (Dosage Range)</th>
<th>Special Considerations and Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>First line(^a)</td>
<td>(\leq 12) yr, 5 mg/day; (\geq 12) yr, 10 mg/day (10–40 mg/day)</td>
<td>Well studied in OCD and bulimia; can increase plasma levels of macrolides, atorvastatin, amphetamine, bupropion, phentermine, antipsychotics, zolpidem, and eszopiclone. Effective for OCD and other anxiety disorders; can increase plasma levels of macrolides, atorvastatin, amphetamine, bupropion, phentermine, antipsychotics, zolpidem, and eszopiclone.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>First line(^b)</td>
<td>(\leq 12) yr, 12.5 mg/day; (\geq 12) yr, 25 mg/day (25–200 mg/day)</td>
<td>Lower risk of drug interactions compared with fluoxetine, but drug interactions still possible; least potent SSRI, so higher end of dosing range may be needed.</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Second line(^c)</td>
<td>(\leq 12) yr, 10 mg/day; (\geq 12) yr, 20 mg/day (20–60 mg/day)</td>
<td>Can increase levels of atorvastatin, amphetamine, and risperidone.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Second line(^d)</td>
<td>(\leq 11) yr, 37.5 mg IR b.i.d.; (\geq 12) yr, 100 mg ER/day (100–400 mg/day)</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) For children and adolescents with major depressive disorder or if obsessive-compulsive disorder (OCD) or bulimia is present.

\(b\) For adolescents with major depressive disorder or if OCD, posttraumatic stress disorder, or generalized anxiety disorder is present.

\(c\) First-line treatment if drug interactions with fluoxetine must be avoided; less evidence for efficacy. SSRI = selective serotonin-reuptake inhibitor.

\(d\) For patients with comorbid attention-deficit/hyperactivity disorder or substance abuse problems or who want to stop smoking. IR = immediate release; ER = extended release.
suicidal ideation or gestures (n = 5), conduct problems or hostility (n = 2), and euphoria (n = 1).46 Five patients in the imipramine group developed the following serious adverse events: maculopapular rash (n = 1), hostility (n = 1), dyspnea or chest pain (n = 1), emotional lability (n = 1), and visual hallucinations or abnormal dreams (n = 1). An analysis conducted by FDA showed that patients taking paroxetine had a higher risk of developing new-onset or increased suicidal behavior compared with those receiving other SSRIs. This prompted FDA to issue a warning in June 2003.47 Due to a lack of established superiority over placebo in treating depression and an increased risk for causing suicidal behaviors when compared with other SSRIs, paroxetine should not be used for the treatment of pediatric depression.

Citalopram. Citalopram has not been shown to be clearly effective in treating depression in children and adolescents, although one controlled trial found it to have significant efficacy over placebo.48 Ninety-three children age 7–17 years with major depression were treated with citalopram and 85 received placebo over eight weeks at 21 different academic sites, including hospitals and clinics.48 The youth had to meet criteria for major depression as defined by a score of ≥20 on the CDARS. The primary response criterion was a score of <28 on the CDARS at the end of the eight-week trial.48 Of the citalopram-treated patients, 36% met the response criterion, compared with 24% in the placebo group.48 There was no significant difference between citalopram (47% of responders) and placebo (45% of responders) on the CGI. The mean effective dosage of citalopram was 25 mg daily.48 Citalopram was considered well tolerated, with abdominal pain, nausea, and rhinitis occurring in over 10% of citalopram-treated patients.48 Two patients in the placebo group discontinued study participation due to lack of response, and two patients in the citalopram group withdrew from the study due to agitation.

In another study, 25 clinically-referred children age 7–18 years participated in a 12-week trial of citalopram to treat recurrent abdominal pain associated with depressive and anxiety symptoms.49 Twenty-one children (84%) were considered responders, with CGI scores of ≤2.49 More studies are needed to determine the role of citalopram in treating depression in pediatric patients. It is an attractive agent, given its lower risk of drug interactions compared with fluoxetine, fluvoxamine, and paroxetine. Currently, escitalopram, the S isomer of citalopram, is being investigated for the treatment of pediatric depression.

Fluvoxamine. Fluvoxamine has not been studied for the treatment of depression in youth, although clinical trials show a positive response for the treatment of anxiety disorders, such as generalized anxiety disorders, social anxiety disorder, separation anxiety, and OCD in children and teens. Fluvoxamine has FDA-approved labeling for use in children eight years or older with OCD.50 It has also been effective in decreasing binging and purging, anxiety, and depressive symptoms associated with bulimia in adolescents.50 Fluvoxamine’s adverse effects are similar to those of fluoxetine, except that it is generally better tolerated when taken at bedtime.23,51 Fluoxetine causes less insomnia when taken in the morning.23,45 Fluvoxamine is a potent inhibitor of the cytochrome P-450 isoenzymes 1A2 and 3A4 and can raise blood levels of drugs that rely on these isoenzymes for metabolism (e.g., caffeine, macrolide antibiotics, some antipsychotics).23,50

Dual-reuptake inhibitors. Bupropion. No published controlled clinical trials have established the efficacy of bupropion for children and adolescents with depressive illness, but two trials have demonstrated its efficacy and safety for adolescents with conduct disorder, substance abuse, and ADHD with or without comorbid depressive illness.51,52 Bupropion is contraindicated in patients with concomitant seizure disorders or eating disorders because it poses an unacceptable risk of seizures.53 It has been suggested as an option for treating refractory depression when two SSRIs trials have failed.54

Venlafaxine. Venlafaxine currently has no literature support for efficacy in pediatric depression.51,55 One placebo-controlled trial of immediate-release venlafaxine was conducted in 33 outpatients age 8–17 years with major depression.56 Children in both groups were rated weekly using the Child Behavior Checklist, CDARS, HAMD, and Children’s Depression Inventory and received psychotherapy, primarily CBT. Each weekly session consisted of 45 minutes of individual and 15 minutes of collateral therapy. Depressive symptoms improved significantly over six weeks on all rating scales, but there was no significant difference between venlafaxine and placebo groups. Dosages of venlafaxine were 37.5 mg daily in children 8–12 years old and 75 mg daily in older adolescents. Low dosages and a short duration of treatment may have contributed to a lack of detectable drug effect with venlafaxine. Mania occurred in one venlafaxine-treated patient, compared with none in the placebo group. Significant nausea was reported in 7 of 16 venlafaxine-treated patients, compared with 1 patient in the placebo group. It is unknown if extended-release venlafaxine would have resulted in less nausea. Adolescents treated with venlafaxine had significantly increased appetite. Improvement in depressive symptoms was likely related to weekly therapy and contact with a clinician. Similar to paroxetine, FDA has found a relatively greater risk of new-onset suicidality with venlafaxine relative to other antidepressants.1
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sence of demonstrated efficacy and concerns over new-onset suicidality, venlafaxine should be reserved for those who do not respond to fluoxetine or sertraline.54

Nefazodone, trazodone, and mirtazapine. No controlled clinical trials have established efficacy for nefazodone and trazodone in children and adolescents with depressive illness. An open-label trial has described nefazodone’s efficacy in treating depression and sleep disturbances.56 Nefazodone carries a warning of hepatotoxicity and is seldom prescribed.57 No controlled clinical trials have demonstrated mirtazapine’s efficacy in treating depression in children and adolescents. One open-label pilot study in 23 adolescents (age 12–18 years) with major depression found a positive response at an average mirtazapine dosage of 32.9 mg daily.58 The most common treatment-emergent adverse effects were tiredness, increased appetite, and dizziness.

Tricyclic antidepressants. Controlled clinical trials have shown no significant difference between tricyclic antidepressants and placebo in the treatment of depression in children and adolescents.12,57 The limitations of tricyclic antidepressant trials include small sample size, possible subtherapeutic dosages, and high response rates to placebo.12,51 The cardiovascular toxicity of tricyclic antidepressants is well established.59 Increases in pulse and diastolic blood pressure and prolongation of the P-R, QRS, and Q-T intervals are well documented in pediatric patients receiving tricyclic antidepressants.59,60 Therefore, the risks of tricyclic antidepressants outweigh potential benefits for most children with depression.12,60 When these drugs are administered to youth with a comorbid condition like ADHD or enuresis, electrocardiograms and vital-sign monitoring are mandatory at baseline, after each dosage increase, and biannually thereafter.12,59

Status of depression treatment in youth. The literature points to suboptimal treatment of depression in youth. Analysis of health service use data over four years (1996–99) in patients age 6–18 years showed that only 1% received treatment for depression, despite an estimated 2–8% rate of depression.10 The majority (79%) of treated children received one or more psychotherapy sessions, and 56.9% received medication.10 Those treated with medication were more likely to suffer from anhedonia, live in large urban communities, have parents who graduated from high school, and have health insurance. Nearly half (47%) of children and adolescents received combined treatment with medication and at least one psychotherapy session. The study found that continuing care was lacking. For example, 33.5% of patients had only one or two psychotherapy sessions. For those who received more, the mean number during a one-year period was 7.7 visits.10 Cumulative evidence on CBT and interpersonal psychotherapy shows that 8–16 weekly sessions are recommended for an optimal outcome.6,61 Of those who were prescribed medication, 15–18-year-old patients were more likely to receive medications than were younger children.10 The duration of medication treatment and the number of medication follow-up visits were not reported.

A study examining the quality of care for Medicaid-covered youth in 1998 found that 42.1% of 507 youth with new episodes of depression received an antidepressant.11 Of these youth, only 28% had three or more follow-up visits in the next three months, despite guidelines that recommend weekly to biweekly follow-up visits in the first six to eight weeks after starting pharmacotherapy.1 Follow-up visits.11 Twenty-nine percent had no further follow-up visits.11 Lack of follow-up has been reported to lead to lack of adherence and lack of antidepressant effectiveness.11

Monitoring and counseling

Follow-up appointments. Both the safety and effectiveness of antidepressants can be enhanced through regular monitoring and counseling by a clinician.12,58 In response to the black-box warning of increased suicidality with antidepressants in youth, FDA has issued guidelines for monitoring.1 These guidelines recommend weekly face-to-face contact with the clinician for the first 4 weeks after starting an antidepressant, with contact every other week for the next 4 weeks, another contact with the clinician after 12 weeks, and as clinically indicated beyond 12 weeks.1 The risk of new-onset suicidal behavior is greatest in the first 2 weeks of treatment. The risk steadily decreases thereafter, with no increased risk after 12 weeks of continuous treatment.62 A medication guide should accompany all antidepressant prescriptions for any indication in youth, including major depression, anxiety disorders (OCD, PTSD, generalized anxiety disorder), and eating disorders.1

The medication guide alerts families and caregivers of the following regarding antidepressant use:

1. There is a risk of suicidal thoughts or actions,
2. Close monitoring and contact with the clinician can prevent suicidal thoughts or actions in your child,
3. Behavioral changes or any increase in suicidal thoughts, attempts, worsening depression, worsening anxiety, panic attacks, agitation, restlessness, aggression, anger, violence, impulsivity, and moodiness can indicate a greater risk for suicide, and
4. There are benefits and risks associated with antidepressant use, and these must be discussed on a case-by-case basis with families and clinicians.1

Additional clinician-provided counseling. Along with counseling patients and their families or caregivers about the risk of suicidality,
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The clinician should spend time discussing depression as a chronic biological illness that is responsive to treatment. The onset of therapeutic benefit of medication or nonpharmacologic treatment can take two to four weeks. The dosage of antidepressant may need to be increased to the maximum tolerated dose for eight weeks before an adequate trial is achieved. Slow dosage adjustment, with increases no more than every two to four weeks, can minimize the risk of behavioral activation, hypomania, and other adverse effects. Once remission is achieved, patients should continue therapy for at least 6–12 months. Maintenance therapy may be needed to prevent relapse. An antidepressant should not be discontinued abruptly (unless mania is the reason for discontinuation), as antidepressant withdrawal symptoms can be severe.

For example, withdrawal symptoms from abrupt discontinuation of an SSRI or venlafaxine can include tearfulness, anxiety, insomnia, nausea, paresthesias, and nightmares. Withdrawal symptoms from tricyclic antidepressants include nausea, vomiting, and diarrhea.

Adverse effects. As a class, all SSRIs have a similar adverse-effect profile. Common adverse effects experienced in 10% or more of individuals who take SSRIs include nausea, diarrhea, restlessness, insomnia, headache, and sexual dysfunction. Uncommon-to-rare adverse effects include extrapyramidal effects (dystonia, pseudoparkinsonism, tardive dyskinesia). Increased bleeding has been reported in children age 8–15 years who developed bruising or epistaxis one week to three months after starting SSRI treatment. Children and adolescents are susceptible to the same adverse effects that adults experience, and all of the adverse effects listed above have been reported in children and adolescents who take SSRIs.

Bupropion can cause similar adverse effects to those of SSRIs (nausea and insomnia) but is not associated with sexual dysfunction. Parents should be counseled on the risk of seizures with bupropion, particularly when bupropion is combined with alcohol or stimulants like amphetamine or cocaine. Venlafaxine’s adverse effects are also similar to those of SSRIs (nausea, insomnia or somnolence, sexual dysfunction), but venlafaxine carries an added dose-related risk of elevated blood pressure. Compared with adults, youth who take antidepressants have an increased risk of behavioral activation, hypomania or mania, and new-onset suicidal thoughts and behaviors.

Clinicians should also counsel patients and their families or caregivers on the following points:

1. Multimodal treatment, including a combination of psychosocial interventions, family therapy, individual CBT for the child, and antidepressant medication, is most effective for treating depression.
2. Fluoxetine should be considered the first-line antidepressant because its efficacy is clearly established and it carries a low risk of new-onset suicidal behaviors.
3. For any youth, the risk of increased suicidal behavior with any antidepressant is highest during the first weeks to months of treatment or if the dosage is increased or decreased.
4. Children or adolescents who develop anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, severe restlessness, hypomania, or mania during antidepressant therapy may be at increased risk of worsening depression or suicidality.
5. Children and adolescents have a greater risk of “switching” to hypomania or mania when taking antidepressant therapy; if this occurs, they should seek help immediately.

Conclusion
Depression in children and adolescents is common. Multimodal treatment includes patient and family education, CBT, and antidepressant medication. The potential benefits of some antidepressant agents outweigh the risks of treatment in adolescents; family and psychotherapeutic interventions are recommended for pre-pubertal children.

References
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