Depression is a major public health problem in the United States, affecting more than 18 million persons and costing more than $43 billion in treatment costs and lost productivity annually [1]. Historically, depression was considered a phenomenon that only adults experienced; however, research has shown that children and adolescents experience a range of depressive disorders [2] similar to adults [3]. Current population point prevalence rates of depressive disorders in adolescents, including major depressive disorder and dysthymia, range from 0.4% to 8.3% [4]. Although rates of these disorders vary depending on the sample studied and the measures utilized [5], they are routinely found to increase dramatically during the adolescent years [6], reaching levels reported in adults by middle to late adolescence [7]. Approximately 5% of adolescents suffer from major depressive disorder at any point in time, 20% have at least 1 episode of clinical depression by age 18 years, and 65% experience transient or less severe depressive symptoms [7]. These statistics are concerning considering the limited availability of psychiatric specialty care [8].

The high prevalence of adolescent depression and the limited availability of adolescent mental health specialists have resulted in a growing need for primary care providers to recognize, diagnose, and treat depression.

**Educational Objectives**

1. Outline an approach to the diagnostic evaluation/workup for an adolescent presenting with depressive symptoms and highlight factors that complicate accurate diagnosis
2. Discuss common etiologies of major depressive disorder in adolescents and describe the expected clinical course and sequelae of adolescent depressive illness
3. Describe indicators of pharmacotherapy, psychotherapy, and/or combined therapy in the treatment of adolescent major depression and the evidence for the efficacy of each strategy
4. Outline the controversy regarding use of selective serotonin reuptake inhibitor medications in adolescents and discuss FDA recommendations for use of these medications in adolescents
5. Discuss how issues of diversity may impact the presentation, assessment, and clinical management of depression in adolescents

**Case Study**

The mother of a 16-year-old girl phones the office of her primary care physician and requests an
appointment for her daughter for evaluation of a potential “hormonal problem,” noting that her daughter is “moody.” An appointment is scheduled. Despite limited information, the physician suspects the possibility of depression and prepares to evaluate the adolescent.

**What is the appropriate workup for an adolescent presenting with a possible depressive disorder?**

**Diagnostic Evaluation of Depressive Disorders**

When an adolescent presents with depressive symptoms, the primary care physician must determine whether the adolescent’s symptoms are (1) representative of transient developmental phenomena, (2) representative of a psychiatric disorder, (3) secondary to a general medical condition, or (4) related to substance use (over-the-counter, illicit, or prescribed) (Table 1). While most differential diagnoses for depression can be ruled out with a thorough history and physical examination [9,13], some laboratory and imaging studies may be necessary. Ultimately, the diagnosis of a depressive disorder is largely clinical in nature and depends on the adolescent meeting diagnostic criteria for 1 of the depressive disorders described in the DSM-IV-TR [14] (Table 2).

The evaluation of depression is comprised of the history and physical examination and can be conceptualized as a biopsychosocial assessment [9,13] (Table 3). No existing technology substitutes for the clinical history and physical examination. Although laboratory findings, imaging studies, and self-report questionnaires may augment the assessment, they cannot confirm the existence of depression.

The interview should include an assessment of the adolescent’s symptoms, both past and present, depressive and otherwise; history of substance use (over-the-counter, illicit, and prescribed); history of self-harm/suicidal behaviors; medical history/issues/concerns; family history; and psychosocial history, including social supports, negative life events/stressors, level of family conflict, and history of abuse and neglect. It is helpful to conduct part of the interview with the adolescent and parent(s)/guardian together and part of the interview separately so that the adolescent can be established as the focus of care [9] and issues of confidentiality can be discussed up front. There are 4 other reasons to take such an approach [9]. First, parents and adolescents do not always agree that a problem exists, as adolescents often minimize their symptoms and fail to recognize their behavior as problematic even though their parents find their symptoms alarming. Second, it is important for the physician to be able to establish rapport and a therapeutic relationship with the adolescent, such that the adolescent does not feel “ganged-up” on and over time becomes more comfortable in admitting difficulties. Third, symptom reports offered by parents and adolescents often differ. Specifically, parents tend to focus on externalizing behaviors that are troublesome to others (eg, oppositionality and defiance), while adolescents tend to focus on symptoms of an internalizing nature—symptoms that cause the adolescent pain and grief but go unnoticed by others (eg, feelings of depression and suicidal thoughts) [19]. Finally, adolescents may be reluctant to share aspects of their symptoms and experiences with their parents in the room and/or may be reluctant to share information that they perceive as shameful or embarrassing. As such, it is important to hear both the adolescent’s and the parent’s perspective on symptomatology separately from each other.

The physical examination should take into account any medical issues or concerns identified during the history, with a focus on ruling out medical explanations of depressive symptomatology. Possible medical explanations include thyroid disease, mononucleosis, chronic fatigue, anemia, diabetes, and neurologic disorders.

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**Table 1. Medical and Psychiatric Conditions Associated with Depressive Symptomatology**

<table>
<thead>
<tr>
<th>Psychiatric disorders with depressive features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>Dysthymia</td>
</tr>
<tr>
<td>Adjustment disorder with depressed mood</td>
</tr>
<tr>
<td>Adjustment disorder with mixed anxiety and depression</td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
</tr>
<tr>
<td>Conduct disorder</td>
</tr>
<tr>
<td>Substance use disorders</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
</tr>
<tr>
<td><strong>General medical conditions with depressive features</strong></td>
</tr>
<tr>
<td>Hypothyroidism/hyperthyroidism</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Mononucleosis</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>Central nervous system disorder (eg, multiple sclerosis, stroke)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substance use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illicit</td>
</tr>
<tr>
<td>Marijuana</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Barbiturates</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Prescribed</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Contraceptives</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
</tbody>
</table>
What factors complicate the diagnosis?

There are 3 major complicating factors in accurately diagnosing depression in adolescents—development, diagnostic overlap, and comorbidity. First, adolescents are constantly growing and experiencing change—physically, cognitively, emotionally, and socially. This development can complicate the diagnosis of depression, as the physician must differentiate normative from pathological psychological processes. Therefore, to make a good assessment, it is crucial to examine the severity of symptomatology as well as the adolescent’s subjective distress and functional impairment. Severe symptoms, high levels of distress, and functional impairment are all indicators of the need to treat.
Second, there is a significant degree of overlap in DSM-IV diagnostic criteria for the different depressive disorders as well as diagnostic overlap in symptom presentation between depressive disorders and a number of medical conditions. Again, this highlights the importance of completing a thorough clinical history focused on gaining a clear understanding of the adolescent’s pattern of symptoms, functional impairment, subjective distress, medical concerns, and psychosocial stressors (Table 3), such that medical and psychological problems can be differentiated (Table 4).

Third, the issue of comorbidity complicates diagnostic clarity. The current scientific literature suggests that depressive disorders rarely occur in a pure form and are generally comorbid with a number of other psychiatric conditions [20]. Birmaher and colleagues [4] noted that 40% to 70% of children and adolescents with major depressive disorder have at least 1 comorbid psychiatric condition. Comorbidity rates for dysthymia are also high [4], with as many as 50% having a preexisting psychiatric disorder and 15% having 2 or more comorbidities [21]. Of specific interest, the degree of comorbidity between major depressive disorder and dysthymia has been found to be 20 times greater than expected by chance [22]. Research suggests that most comorbid psychiatric diagnoses, including dysthymia, attention-deficit/hyperactivity disorder, anxiety disorders, personality disorders, and substance use difficulties, have a tendency to precede and/or coincide with the onset of a major depressive episode [20–25]. The exception is with conduct difficulties, where some research suggests that conduct problems follow the depression [26], and other research suggests they precede it [20]. Regardless, depression generally is not “pure,” and such comorbidity significantly impacts diagnostic clarification.

**Initial Patient Visit and History**

The 16-year-old girl attends the appointment accompanied by her mother. In meeting, the mother is...
quite talkative and outspoken, while the adolescent appears quiet and sullen. Mother reports a 3-month history of increased irritability and “moodiness” as well as episodes of outward defiance and oppositionality (eg, refusing to attend school and staying out past her curfew). The frustrated mother states, “I just want my sweet daughter back” and notes that she is weary of her daughter’s “mood swings.” Mother further reports that she cannot understand why her daughter seems “stressed” and “anxious” over “the most minor things” and wonders whether this could be a “hormonal” problem. While the teen does not verbally dispute anything her mother says, she is notably annoyed.

Further questioning reveals that the girl has a host of depressive, anxious, and oppositional symptoms. Over the last 4 months, she has felt depressed “most of the time” and has not been interested in “much of anything.” She has quit her soccer team and did not go out for the school basketball team, even though these were activities she previously enjoyed. Both mother and daughter report a 3-month history of extremely low energy, sleeping in excess of 12 to 14 hours per day, and often taking naps after school. With this, the girl suspects recent weight gain, stating “I can’t fit into any of my pants anymore,” and her mother notes that she has been “continuously hungry over the last few months.” The teen notes that she has had difficulty concentrating lately, with some decline in grades, but is hesitant to

Table 4. Differential Diagnosis: Major Depression versus Other Conditions—Common and Distinguishing Symptomatology

<table>
<thead>
<tr>
<th>Psychiatric or Medical Diagnosis</th>
<th>Common Features with Major Depression</th>
<th>Distinguishing Features from Major Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysthymia</td>
<td>Depressed mood, irritability, appetite disturbance, sleep disturbance, fatigue, poor concentration</td>
<td>Slower and more insidious onset; chronic duration (eg, at least 1 year)</td>
</tr>
<tr>
<td>Adjustment disorder with depressed mood</td>
<td>Depressed mood, irritability, poor concentration, fatigue</td>
<td>Presence of onset within 3 months of psychosocial stressor; symptoms tend to be less severe than observed in MDD; does not meet criteria for MDD or dysthymia</td>
</tr>
<tr>
<td>Depression not otherwise specified</td>
<td>Any number of MDD symptoms, including depressed mood, anhedonia, appetite disturbance, sleep disturbance, fatigue, poor concentration, feelings of worthlessness and guilt</td>
<td>Does not meet criteria for any other depressive disorder</td>
</tr>
<tr>
<td>Mood disorder due to a general medical condition</td>
<td>Any number of MDD symptoms, including depressed mood, anhedonia, appetite disturbance, sleep disturbance, fatigue, poor concentration, feelings of worthlessness and guilt</td>
<td>Depressive symptoms occur in the context of an identifiable medical condition</td>
</tr>
<tr>
<td>Substance-induced mood disorder</td>
<td>Any number of MDD symptoms, including depressed mood, anhedonia, appetite disturbance, sleep disturbance, fatigue, poor concentration, feelings of worthlessness and guilt</td>
<td>Depressive symptoms occur in the context of the initiation or the withdrawal of any substance</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Depressed mood, fatigue, irritability, decreased libido, weight gain</td>
<td>Presence of dry skin, coarse hair, cold intolerance, constipation, muscle cramps, and/or hair loss; absence of suicidality, anhedonia, diminished concentration, worthlessness/guilt</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>Fatigue, poor concentration, poor sleep</td>
<td>Presence of muscle pain, headaches, multijoint pain, and/or tender lymph nodes; absence of suicidality, anhedonia, worthlessness/guilt</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fatigue, irritability, extreme hunger or unusual weight loss</td>
<td>Presence of frequent urination, excessive thirst, blurry vision; absence of suicidality, diminished concentration, anhedonia, worthlessness/guilt</td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>Fatigue, poor appetite</td>
<td>Presence of fever, sore throat, enlarged lymph nodes, sore muscles, and/or enlarged spleen; absence of suicidality, diminished concentration, anhedonia, worthlessness/guilt</td>
</tr>
<tr>
<td>Central nervous system disorder</td>
<td>Depressed mood, fatigue, poor concentration, psychomotor agitation/retardation</td>
<td>Presence of neurologic insult, visual disturbance, paralysis; absence of absence of suicidality, anhedonia, worthlessness/guilt</td>
</tr>
</tbody>
</table>

MDD = major depressive disorder.
discuss school issues in front of her mother. She reports feeling “bad” about herself, and believes she is “a failure and a loser.” When questioned about suicidality, both mother and daughter deny this is an issue. With regard to symptoms of anxiety, the girl states that she has felt “worried about everything” including school and peer relationships. She reports being worried about what other teens think of her, and notes that she frequently gets preoccupied with past social interactions and whether she said or did “the right thing.” As a result, the teen notes she has been “hiding out from everyone and everything.” When asked about somatic complaints, the girl endorses worries that she might have a “horrible disease” as she has been having a lot of head, back, and stomach pain recently. In terms of oppositional symptoms, mother notes that in the last 3 months, she has struggled to get her daughter out of bed in the morning, and that in the months prior to this, her daughter frequently defied house rules, ignored her curfew, and came home “tipsy” a few times. Neither mother nor teen offer a hypothesis regarding the development of the girl’s symptoms and deny any significant psychosocial stressors. At the same time, the daughter is notably uncomfortable with the conversation and appears reluctant to share further information.

In meeting alone with the physician, the girl alludes that there are some things she cannot tell her mother for fear that her mother will be angry. The adolescent is hesitant to talk and focuses on the idea that she must have a “horrible disease.” When asked why she suspects this, she states, “I just haven’t been feeling well—I often have a headache, a stomachache, or both . . . all I really feel like doing is sleeping.” In following up on these concerns, the girl denies decreased appetite, but again notes weight gain, and begins to cry, stating “I think I might be pregnant . . . my parents will hate me forever.” She goes on to reveal that about 6 months ago, she met an older boy at school whom she started dating and with whom she has always had a hard time telling “no” for fear of being “dumped.” She notes she did some things with him she did not really feel comfortable doing and that she knew upset her parents, such as not coming home on time and getting drunk. When asked if she has had a sexual relationship with this boy, she states that he pressured her into having intercourse approximately 3 months ago. She describes the experience as “awful” and sobs as she reports that he quit talking to her afterwards. She notes that he will not return her phone calls or acknowledge her at school, and that he has started dating one of her close friends. She is worried that she is pregnant “because there was no protection” and further notes she feels like everyone at school is looking at her and thinking that she is a “real loser.” She acknowledges these stressors coincide with the onset of her symptoms.

With regard to physical symptoms, she endorses headaches, stomachaches, weight gain, and fatigue that started after the sexual experience. Although she reports some diarrhea, she denies nausea and vomiting, reports her last menstrual period was about 5 or 6 weeks ago, and denies other symptoms commonly associated with pregnancy. She denies the use of recreational drugs in the last 3 months as well as the use of any medications outside of minocycline for acne and ibuprofen for headaches.

The family history is significant for depression in the girl’s paternal grandfather and anxiety in her mother.

Physical Examination

On examination, the patient is a white girl of normal height and weight, despite a 10-lb weight gain. She is well-groomed and cooperative, but her mood is sad and worried. Her thoughts are linear and goal-directed. Her speech is of normal rhythm and rate, although quiet. She appears somewhat tired and is tearful when talking about her recent experiences. She denies suicidal ideation, plans, or attempts, but notes “sometimes I wish I were dead because then I would not have to deal with all of this.” She further notes great worry about what her parents would think of her if they knew what happened and states “I just want to feel better.” Her physical examination is within normal limits.

Laboratory Data

Laboratory testing results, including thyroid-stimulating hormone, are within normal limits, and a serum pregnancy test is negative.

Diagnosis

The physician makes a diagnosis of major depressive disorder, with a rule out of anxiety disorder not otherwise specified.

- What are common etiologies of major depressive disorder in adolescents?

Etiologic factors in the development of depressive disorders in adolescents are not well understood. Purported etiologic contributors can be classified into 3 broad categories: biological, psychological, and social. Yet, while there are several proposed etiologies with supporting research evidence, no one theory or “cause” has emerged in explaining the phenomenon. As such, adolescent depression is currently best conceptualized as a heterogeneous disorder whose pathogenesis is explained by multiple factors and processes [4]. That is, while depression may be more heavily related to family genetic history for one adolescent, it may be better explained by psychosocial factors for another, and a combination of the 2 for yet another. Proposed biological causes of adolescent depression include genetics/parental psychopathology [27–29] and...
ADOLESCENT DEPRESSION

the dysregulation of any one of a number of physiologic systems within the body, including the serotonergic system [30], the hypothalamic-pituitary axis [31], and growth hormone secretion [32]. Proposed psychosocial etiologies include stressful life events [33], depressogenic and negative cognitive styles [34,35], and conflicted and disturbed family environments [36].

- What is the expected clinical course and sequelae?

The mean length of a major depressive episode in adolescents ranges from about 6 to 9 months [37–39], with the vast majority of such episodes remitting within 12 to 24 months of onset [38–42]. Although most episodes remit within about 2 years, up to 10% of adolescents will experience a more protracted episode [38,40,42]. Regardless of when remission occurs, there is a high rate of recurrence, with up to 69% of adolescents experiencing a relapse within 2 to 5 years [37–39,43,44]. Research evidence also suggests that nearly 20% will go on to develop bipolar disorder [39]. Risk factors for the recurrence of major depressive disorder include female gender, multiple previous episodes, family history of recurrent major depressive disorder, and borderline personality disorder symptoms [45]. Risk factors for the later development of bipolar disorder include depression with an early onset, depression with psychomotor and/or psychotic features, a family history of bipolar disorder, a genetic loading for mood disorders in general, and/or pharmacologically induced hypomania [4]. Whereas major depressive disorder generally remits within 24 months, dysthymia by definition has a much more protracted but less severe course. In general, dysthymia has a mean episode length of 33 to 48 months [21,22] and appears to heighten the severity of the illness. In addition, dysthymia has a relapse rate of 69% within 2 to 5 years [37–39,43,44].

Research suggests that the statistics reported above are impacted by comorbidity. Specifically, the results of a number of investigations show that comorbidity negatively impacts not only the severity and duration of the depressive episode but can also be associated with the recurrence of depression, increased levels of suicidality, increased rates of social dysfunction, and higher utilization of mental health services [25,41,45–50].

The sequelae of adolescent depressive disorders are not well understood. On one hand, the consequences appear vast, as depression during this developmental period is associated with a host of psychosocial deficits, including poor global and adaptive functioning, academic and occupational impairment, disrupted interpersonal relationships, early childbearing, reduced life satisfaction, and substance abuse/dependence [39,51–55]. On the other hand, such findings must be considered in the context of 2 major caveats. First, such psychosocial deficits tend to be correlates of adolescent psychopathology in general. Second, even though such psychosocial deficits tend to be correlates of adolescent psychopathology in general, many of the associations are reported to disappear when a number of other variables, such as nonmood disorder, major depressive disorder recurrence, functioning in adolescence, and current mood state, are controlled for statistically [53]. Although further research is needed to clarify the sequelae of adolescent depression, adolescents with poor premorbid psychosocial functioning, concurrent or subsequent nonmood disorders, and/or recurrent major depressive disorder may be at heightened risk for future difficulties. These data highlight the importance of early intervention to limit the depressive episode and potentially curtail future problems.

- What are the first steps in the treatment of major depressive disorder?
- What type of treatment is most efficacious—medication, psychotherapy, or both?

Treatment

As is the case in managing any mental health concern, the first step in treatment is to ensure the safety of the patient and others. If necessary, hospitalization for acute suicidality or homicidality should be sought. When such concerns are not of imminent relevance, outpatient treatment may proceed. With this, the primary care physician is faced with recommending appropriate treatment. The American Academy of Child and Adolescent Psychiatry practice parameters for the treatment of children and adolescents with depressive disorders call for the use of a multimethod treatment approach that not only takes into account the severity of the illness and the motivation of the patient and the patient’s family but also the severity of other psychiatric and/or medical conditions and the importance of providing treatment in the least restrictive safe environment [56]. In line with these recommendations, with some limitations, empirical studies have supported both psychopharmacologic and psychosocial interventions for major depressive disorder in adolescents.

Psychopharmacologic Options

Over the last several years, psychopharmacologic treatment of depression in adolescents has become increasingly common [57,58]. Despite numerous trials with negative results prior to 1997, a variety of antidepressant medications were prescribed, including tricyclic antidepressants and monoamine oxidase inhibitors [43]. In 1997, the first double-blind,
placebo-controlled trial of the selective serotonin reuptake inhibitor (SSRI) fluoxetine showed the drug to be efficacious in the treatment of youth with major depressive disorder [43]. Following a second positive fluoxetine study [59], the U.S. Food and Drug Administration (FDA) approved fluoxetine for treatment of major depression in children and adolescents. Although a number of other SSRI medications, including paroxetine, sertraline, citalopram, and venlafaxine, have been studied in child and adolescent samples (Table 5) [43,59–63], the results have been somewhat difficult to decipher [60–62,64]. While there is generally some statistical evidence that SSRI medications are efficacious in the treatment of depressed adolescents (eg, response rates ranging from 36%–70%) [43,61], clinical significance is sometimes lacking. Specifically, even though research has revealed statistically significant findings, there have been high placebo response rates and minimal clinical differences between medication and placebo groups (eg, 36% versus 24% with citalopram) [43,61,62]. Other research has shown that the overall effect of some SSRI medication is low [62], and still other studies have offered no evidence that SSRI medication is beneficial in adolescent populations [64,65]. Despite these mixed results, SSRIs have emerged as the psychopharmacologic treatment of choice with depressed youth.

In an effort to facilitate an approach to the treatment of depressed youth that was both systematic and empirically informed, the Texas Children’s Medication Algorithm Project published a set of guidelines outlining various psychopharmacologic treatment options [66]. Although these guidelines were developed for use in the public mental health sector [66], they appear to have applications in the primary care setting. A graphic depiction of this algorithm can be accessed online at www.dshs.state.tx.us/mhprograms/mddalgo.pdf. The algorithm is intended for the treatment of children and adolescents with major depressive disorder that is severe enough to warrant intervention with psychotropic medications. It highlights the importance of assessment and family considerations in determining whether to initiate medication, psychotherapy, or both [66]. In general, the algorithm guides practitioners through a progressive series of medication treatment options that initially involve monotherapy with medications that are safe, have low toxicity, and have favorable side effect profiles [66]. In cases where the adolescent does not show symptom improvement, however, the algorithm moves through other options that progressively become more complicated, pose greater risks for side effects, require closer monitoring by physicians, and are less empirically supported [66]. As such, these may represent natural times in which primary care physicians would refer the adolescent for specialty psychiatric care.

**Psychotherapeutic Options**

Even though research focusing on psychosocial interventions for depressed youth is growing rapidly, only a small number of controlled studies assessing such interventions have been performed. Currently, the psychotherapeutic treatment literature for depression comes from a variety of theoretical orientations and approaches, ranging from social skills and supportive group treatments [67] to individual psychodynamic [68], interpersonal [69] and cognitive-behavioral treatment [70], to family therapy [71]. To date, cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) are the most widely studied and efficacious treatments studied in controlled trials.

CBT has been delivered to adolescents in both individual and group formats with remarkably consistent results. A number of individual studies and 3 meta-analytic studies have deemed CBT an effective treatment for adolescent depression [70,72,73]. Improvement rates in individual studies range from 54% to 67% [74–76], and the magnitude of reported effect sizes

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**Table 5. Published Double-Blind Placebo-Controlled Trials of Antidepressants in Treatment of Major Depression with Positive Results**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of Treatment, wk</th>
<th>Participants, n</th>
<th>Mean Dose, mg</th>
<th>Responders, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine [43]</td>
<td>8</td>
<td>96</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>Fluoxetine [59]</td>
<td>9</td>
<td>419</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>Fluoxetine (TADS) [63]</td>
<td>12</td>
<td>439</td>
<td>33.3</td>
<td>60</td>
</tr>
<tr>
<td>CBT + fluoxetine</td>
<td></td>
<td></td>
<td>28.4</td>
<td>71</td>
</tr>
<tr>
<td>Paroxetine [60]</td>
<td>8</td>
<td>275</td>
<td>28</td>
<td>63</td>
</tr>
<tr>
<td>Sertraline [61]</td>
<td>10</td>
<td>376</td>
<td>131</td>
<td>69</td>
</tr>
<tr>
<td>Citalopram [62]</td>
<td>8</td>
<td>176</td>
<td>24</td>
<td>36</td>
</tr>
</tbody>
</table>

CBT = cognitive behavioral therapy.
In meta-analytic studies range from 0.41 (small) to 1.70 (large) [70,72,73]. Although CBT appears to have a clear advantage over other treatments in the acute management of major depressive disorder in youth [76,77], this initial advantage tends to dissipate with time such that there is no long-term advantage to CBT with regard to remission, recovery, recurrence, and overall functioning [76,78]. These findings have led some investigators to examine whether booster sessions following acute treatment may help adolescents maintain gains. Booster sessions have not been found to reduce the recurrence rate of depression at follow-up, even though they appear to speed the recovery of adolescents who remain depressed following acute treatment [75].

IPT has been utilized in both clinic and school settings. Across these different settings, IPT has been shown to be efficacious in reducing depressive symptoms and improving social functioning and interpersonal problem solving in acutely depressed adolescents [69,79–81]. While CBT and IPT have been the focus of empirical investigation in treating depressed adolescents with psychosocial/psychotherapeutic interventions, the importance of family work in the treatment of depressed adolescents cannot be underestimated. To this end, some investigators have begun to highlight the importance of family work in depression treatment [82,83], and others have begun to develop specific family-based interventions (Family Therapy for Depressed Adolescents/Attachment-Based Family Therapy [71,84] and Stress Busters [85]). Family interventions appear to be promising in the treatment of depressed youth and should be part of treatment for all depressed adolescents.

**Combined Pharmacotherapy and Psychotherapy**

In examining psychopharmacologic and psychotherapeutic interventions as a whole, the results are quite similar. Regardless of the type of intervention, approximately 40% of depressed youth are nonresponders to treatment [60,70], and of those who respond to acute treatment, relapse rates within 1 year following treatment are significant [78]. These statistics highlight the need for researchers to continue to identify and study innovative treatment options for depressed adolescents and bring into question whether treatments that combine pharmacotherapy with psychotherapy may result in better outcomes. In the only randomized controlled trial combining medication with psychotherapy in the treatment of depressed youth, investigators in the Treatments for Adolescents with Depression Study compared groups of depressed adolescents receiving medication alone (fluoxetine), psychotherapy alone (CBT), combined treatment (fluoxetine + CBT), or placebo [63]. This landmark study, which was the first to pit pharmacotherapy against psychotherapy in a randomized controlled trial, found that fluoxetine combined with CBT had a 71% response rate and was superior to fluoxetine alone (63%), CBT alone (43%), and placebo (35%) in the acute treatment of depressed adolescents [63]. The study represents the only available data directly comparing pharmacotherapy and psychotherapy within the same study design and suggests that combined treatment may be most efficacious.

- **What approach can be used to choose among the treatment options?**

Questions remain regarding which treatments are best for which depressed adolescents. While there are some data to support both psychopharmacologic and psychosocial interventions, limited response rates for both types of treatment have, at least in part, led to the recommendation for the use of combined treatment [56]. This recommendation makes sense given the severity of the costs of depression, both psychosocial and academic, as well as the psychosocial and developmental context in which depressive disorders emerge [56]. At the same time, however, the approach is limited by the lack of a complete understanding of how different treatments compare with each other, as well as the lack of a complete understanding as to which adolescents will benefit most from which treatments, particularly when a combined treatment approach is not viable. Although there is not a specific algorithm regarding which treatments to choose in which situations, pharmacotherapy should be strongly considered when there is a positive family history for mood disorder; positive family history for response to antidepressant medications; neurovegetative signs and symptoms of depression, such as changes in sleeping and eating patterns; severe, chronic, and/or recurrent depression; poor or limited response to psychotherapy alone; and/or limited resources [66]. On the other hand, psychotherapy should be strongly considered in the presence of severe psychosocial stressors, poor medication compliance or refusal to take medications, suicidality, and/or poor or limited response to pharmacotherapy alone [66].

These are general guidelines, not hard and fast rules. It should be recognized that pharmacotherapy often offers adolescents enough symptom relief to allow them to more productively engage in psychotherapy. Ultimately, the best clinical decisions regarding treatment approaches and options—whether pharmacotherapy, psychotherapy, or combined—should be made jointly and in collaboration with the adolescent and his/her parent/guardian once all options and their benefits and risks have been fully discussed [66].
**CASE-BASED REVIEW**

**Initiation of Therapy**

The physician talks with the patient and her mother regarding the diagnosis, reviews issues related to possible etiologies, discusses clinical course and potential sequelae, offers information regarding treatment, and develops a collaborative treatment plan. Given the fact that there is reason to believe that both pharmacotherapy and psychotherapy could be important aspects to the girl’s treatment (eg, neurovegetative symptoms, presence of severe psychosocial stressor), the physician recommends combined treatment, and the family agrees. The physician prescribes fluoxetine 10 mg orally daily with a plan to increase the dosage to 20 mg orally daily after a week or 2, reviews the side effects of the medication, encourages the patient to communicate any intent to discontinue the medication, and offers a referral for psychotherapy. A follow-up appointment is scheduled in 1 week.

**Between-Visit Message from Mother**

Three days after developing and initiating the treatment plan with the family, the physician receives a message from the patient’s mother stating that after doing some internet research, she is worried that fluoxetine may cause her daughter to become suicidal. She requests a return call as soon as possible and notes that she may not offer her daughter any more medication until she talks with the physician further.

- Are there any special considerations that need to be made in the assessment and treatment of depressed adolescents?

**The SSRI Medication Controversy**

Recently debate has arisen in both Great Britain and the United States concerning the use of SSRIs in treating children and adolescents. This debate centers on concerns related to the number of unpublished SSRI trials showing negative results, the extent of the benefit that children and adolescents actually receive from SSRIs in published trials showing positive results, and the possible link between SSRI use and mood-related side effects, including suicide attempts. In June 2003, the British Medicines and Healthcare Products Regulatory Agency (MHRA) took formal regulatory action and declared paroxetine contraindicated for the treatment of major depression in individuals under age 18 years [86]. The FDA followed suit approximately 1 week later, recommending that paroxetine not be used in youth [87]. Since the MHRA and FDA took regulatory action in June 2003, the MHRA has further declared a number of other SSRI medications, including venlafaxine, citalopram, S-citalopram, sertraline, nefazodone, and mirtazapine, contraindicated in the treatment of depressed youth, noting that the benefits of treatment with these agents do not outweigh the risks [88].

Parallel with the MHRA review process, the FDA also reviewed the use of SSRI medications with children and adolescents. U.S. academicians took exception to the cautionary recommendations that came out of these reviews, noting that the interpretation of the data was flawed because there were no statistically significant differences in suicidality rates between drug and placebo conditions in the studies examined by the MHRA and FDA [89,90]. Specifically, the aggregated compilation of data on over 4400 children and adolescents treated in controlled trials with SSRIs revealed a risk of mood-related side effects in 2% of youths treated with placebo versus 4% in youth on active drug, with no completed suicides. Nevertheless, the FDA issued a Black Box warning regarding an increased risk of suicidal behavior in children and adolescents treated with antidepressant medication and a Medication Guide for Families that recommends close monitoring (eg, once a week for the first 4 weeks, every 2 weeks for the next 4 weeks, after 12 weeks of antidepressant use, and more often if problems or questions arise) when a patient is placed on antidepressant medication [91].

While the academic community in the United States and the FDA remain at odds regarding this issue, there is agreement that when antidepressants are used, practitioners must fully inform their patients and families of possible side effects and devote increased attention during follow-up to signs of suicidality and the clinical worsening of symptomatology [91]. In a British meta-analysis, Whittington and colleagues concluded that fluoxetine is the only SSRI medication that has a favorable risk-benefit ratio [92]. In addition, fluoxetine is the only medication that has an FDA indication for the treatment of major depression in youth [91].

**Suicidality and Self-Harm**

Although adolescent suicide rates have steadily decreased over the past 15 years, they nevertheless remain approximately 3 times greater than rates 50 years ago [93]. In 2002, the last year for which data are available, there were approximately 1.23 suicides per 100,000 children and adolescents aged 10 to 14 years, and 7.44 suicides per 100,000 adolescents aged 15 to 19 years, translating to approximately 1800 completed suicides among 10 to 19 year olds [93].

As suicidal ideation is relatively common in both male and female adolescents, and far more adolescents will express suicidal ideation than will attempt or commit suicide [94], it is important for physicians to be aware of the factors/variables that appear to increase an adolescent’s risk of completed suicide. For example, age and gender are related to risk. Compared with younger adolescents, older adolescents are at higher risk, as are males, compared with females [95]. Explanations for these factors center on the higher rates of psychopathology in older adolescents, particularly mood
disorders and substance use/abuse, and the more lethal methods of suicide that males tend to choose, such as firearms [94,95]. As research suggests that the vast majority of adolescents who commit suicide have a diagnosable psychiatric disorder at the time of their death [94], it is of further importance for the primary care physician to assess psychiatric symptomatology and complete a suicide assessment in adolescents endorsing such difficulties. In addition to age and gender, other risk factors include previous suicide attempts, stressful life events, poor parent-child communication, hopelessness, family history of suicidal behavior and mood disorder, exposure to real or fictional accounts of suicide, exposure to family violence, impulsivity/agitation, homosexuality, and the availability of means/methods [94].

It should also be noted that self-mutilation, such as cutting, has become very prevalent in the adolescent population. Specifically, it is estimated that approximately 14% of adolescents in the general population [96] and 61% of adolescents in psychiatric inpatient populations [97] engage in these behaviors. In study samples of psychiatric inpatients, adolescent female self-mutilators outnumber their adolescent male counterparts by a ratio of approximately 3 to 1 [98,99]. Longitudinal data regarding which of these adolescents actually go on to commit suicide, however, is lacking.

**Phone Call Returned to Mother**

During a phone conversation, the patient’s mother reiterates her concern that treatment with SSRI medication may cause her daughter to become suicidal. The physician reviews the risks and benefits of taking medication, highlights the fact that her daughter was prescribed the one medication approved for use with depressed adolescents, and discusses her daughter’s relative risks (eg, denied current suicidality on assessment). The physician also highlights the fact that suicidality is highly correlated with depression, whether taking SSRI medication or not, and encourages the mother to be mindful of any suspicious behaviors on the part of her daughter (eg, giving away belongings, increased hopelessness, and suicidal talk). She also encourages the mother to act preventatively and safeguard her home from firearms (if present) and other accessible methods, such as medications. She assures the mother that the assessment of suicidal thoughts, feelings, and behaviors will occur during follow-up visits and during her daughter’s visits to her therapist. Mother’s concerns are allayed with this discussion and the treatment plan proceeds.

- What would have been the impact if the adolescent in this case was of a different gender, culture, or sexual orientation?

While depressive disorders occur at similar rates for girls and boys during childhood, this shifts with puberty. More specifically, while slightly more females than males are depressed between the ages of 13 and 15 years, this difference grows during middle to late adolescence, such that depressed girls begin to outnumber depressed boys by a ratio of 2 to 1 [100], similar to rates in adults [101]. This has led some investigators to suggest that middle to late adolescence is a critical time period in the development of depression [100]. Several theories have been offered as to why this may be the case, highlighting a variety of potential biologic (eg, effect of gonadal hormones on limbic system hyperactivity [102]), psychological (eg, personality characteristics [103]), and social (eg, interpersonal relationships/conflicts [104]) contributors. Scientific evidence suggests that the gender difference may best be explained by the convergence and interaction of several factors, some of which are present prior to early adolescence (eg, personality factors such as ruminative coping), and some of which emerge with the increasing challenges of adolescence (eg, social and biological factors, such as parent and peer expectations and puberty) [103–105].

While gender differences in the prevalence of depression that emerge with adolescence are well documented in the scientific literature, data concerning differences in the ethnic and cultural differences in prevalence are somewhat limited. Asian-American adolescents appear to be at lowest risk (1.3%–5.6%) for depressive disorders, followed by Anglo-American adolescents (4.3%–9.6%), African-American adolescents (6.1%–13.4%) and Mexican-American adolescents (9.0%–16.9%) [106,107]. Females tend to be at higher risk than males across all ethnic/cultural groups [106,107]. Outside of identifying racial/ethnic groups that are at higher risk for depression than others, it is also important for primary care physicians to know how cultural factors may impact the presentation of depression in adolescents, as well as the acceptability of treatments to depressed adolescents and their families [9]. Choi [108] provides a comprehensive review of this ethnocultural context, highlighting several important issues related to African-American, Asian-American, and Hispanic-American adolescents. More specifically, African-American adolescents may be more likely to express their depression through a variety of behaviors that are traditionally thought to be externalizing in nature (eg, anger, aggression, and hostility), which often leads to the misdiagnosis of schizophrenia [108]. Hispanic-American adolescents may utilize a variety of culture-bound syndromes and expressions to describe their emotional distress, including mal del cerebro o de la mente (bad in the brain or in the mind), locura (craziness), and nerviosidad (nervousness), while Asian-American adolescents may express their depression through internalizing symptoms, such as social withdrawal, introversion, and a host of vague somatic complaints (eg, headache, abdominal pain, and musculoskeletal pain) [108].
The final area in which the assessment and treatment of depressed adolescents may be impacted by diversity is sexual orientation. As emerging sexuality is a central issue for all adolescents, it has been posited that homosexual adolescents may be at heightened risk for depression and suicide, as they are not only faced with the general challenges of adolescence, but are also faced with managing the stigma associated with “coming out” and developing an identity as a gay man or lesbian woman [109]. Research evidence suggests that gay and lesbian youth are more than 2 times more likely to attempt suicide than their heterosexual peers [110].

• At what point is it appropriate to refer to a psychiatrist for specialty care?

Although it is quite reasonable for adolescent depression to be managed by primary care physicians with adequate training and experience, referral to a child and adolescent psychiatrist can be undertaken in response to any one of a number of questions or concerns. Referral to a child and adolescent psychiatrist is specifically recommended when the physician feels uncomfortable managing the depressed adolescent and/or the adolescent’s depression is complicated by comorbidity, mania, suicide attempts/self-harm, psychotic behavior, recurrent episodes, severe functional impairment, and/or treatment resistance [13].

1 Week Later

One week into treatment, the patient notes that she does not really feel better but denies medication side effects and states that she thinks she will like her new therapist, whom she she has only met once. The physician follows up on a variety of symptom-related issues, including suicide, reviews the fact that antidepressant medications take time to work, and encourages ongoing participation in therapy. A return visit is scheduled in 1 week, and the physician obtains consent to talk with the patient’s new therapist.

CONCLUSIONS

Adolescent depression represents a serious mental health issue that is increasingly coming to the attention of primary care physicians. Not only do a large number of adolescents experience a major depressive episode by age 18 years, many others experience less severe and transient depressive symptoms [7]. Depression is often associated with functional impairment and other negative outcomes, including recurrent episodes and suicide. At the same time, however, effective treatments do exist. As the primary care physician often represents the first-line of treatment for depressed adolescents, the importance of adequate training regarding the assessment and diagnosis of depression in adolescents cannot be underestimated.

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References

ADOLESCENT DEPRESSION


ADOLESCENT DEPRESSION


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Current Perspectives on the Diagnosis and Treatment of Adolescent Depression in the Primary Care Setting

DIRECTIONS: Each of the questions below is followed by 5 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. What are complicating factors in accurately diagnosing depression in adolescents?
   (A) Development
   (B) Diagnostic overlap
   (C) Comorbidity
   (D) B and C only
   (E) All of the above

2. Which of the following statements is FALSE?
   (A) Biologic, psychological, and social factors are all purported to be possible etiologic contributors to adolescent depression.
   (B) Adolescent depression is best conceptualized as a homogenous disorder whose pathogenesis is explained only by biological factors and processes.
   (C) While the mean length of an adolescent major depressive episode ranges from 6 to 9 months, 10% of depressed adolescents will experience episodes lasting more than 2 years.
   (D) Within 2 to 5 years of remission, approximately 69% of adolescents will experience a recurrence of major depression.
   (E) Risk factors for the later development of bipolar disorder include: early onset depression, depression with psychomotor and/or psychotic features, a family history of bipolar disorder, a genetic loading for mood disorder, and pharmacologically induced hypomania.

3. Pharmacologic interventions should be considered when there is ___________ and ___________, whereas psychotherapeutic interventions should be strongly considered when there is ___________ and ___________?
   (A) A positive family history for mood disorders and neurovegetative signs and symptoms; the presence of severe psychosocial stressors and suicidality.
   (B) The presence of severe psychosocial stressors and suicidality; a positive family history for mood disorders and neurovegetative signs and symptoms.
   (C) Severe, chronic, and/or recurrent depression and the presence of severe psychosocial stressors; poor medication compliance and poor or limited response to pharmacotherapy alone.
   (D) Severe, chronic, and/or recurrent depression and poor or limited response to psychotherapy alone; poor medication compliance and poor or limited response to pharmacotherapy alone.
   (E) A and D

4. Which of the following statements is TRUE?
   (A) The FDA has issued a Black Box warning regarding an increased risk of suicidal behavior in children and adolescent treated with antidepressant medication
   (B) Fluoxetine is the only SSRI medication that has an FDA indication for the treatment of major depression in youth
   (C) The FDA has issued a Medication Guide for Families highlighting a series of recommendations regarding how closely antidepressant medication should be monitored
   (D) A and C only
   (E) All of the above

5. Which groups of youth are more likely to be at heightened risk for depression?
   (A) Female, Asian-American, and heterosexual youth
   (B) Male, Mexican-Americans, and homosexual youth
   (C) Female, Mexican-American, and homosexual youth
   (D) Female, African-American, and homosexual youth
   (E) Male, Anglo-American, and heterosexual youth
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   __ Yes __ No

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