

Clinical Practice

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

ADOLESCENT DEPRESSION

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A 16-year-old boy is brought by his parents to his primary care physician because of a decline in school performance, which began at least three years earlier and has become more severe in the past year. He reports boredom, a lack of enjoyment and motivation, poor self-esteem, a feeling of hopelessness, difficulty sleeping, poor concentration, and passive thoughts of suicide without a plan or intent. How should he be treated?

THE CLINICAL PROBLEM

This patient presents with a clear picture of major depression, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, of the American Psychiatric Association (Table 1).¹ In children and adolescents, depression is not always characterized by sadness, but instead by irritability, boredom, or an inability to experience pleasure. Depression is a chronic, recurrent, and often familial illness that frequently first occurs in childhood or adolescence. Any child can be sad, but depression is characterized by a persistent irritable, sad, or bored mood and difficulty with familial relationships, school, and work. In the absence of treatment, a major depressive episode lasts an average of eight months. The risk of recurrence is approximately 40 percent at two years and 72 percent at five years.² Longer depressive episodes occur in patients who have a dysthymic disorder (a milder, but chronic and insidious form of depression) that gradually evolves into major depression. More prolonged episodes are also associated with coexisting psychiatric conditions, parental depression, and parent-child discord.²

At least 20 percent of those with early-onset depres-

TABLE 1. CRITERIA FOR MAJOR DEPRESSIVE EPISODE.*

A major depressive episode is indicated by the presence of five or more of the following symptoms nearly every day during the same two-week period, representing a change from the previous level of functioning:
Depressed mood most of the day
Markedly diminished interest or pleasure in all or almost all activities
Clinically significant weight loss in the absence of dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month) or a decrease in appetite†
Insomnia or hypersomnia
Observable psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Diminished ability to think or concentrate or indecisiveness
Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

*Criteria are from the American Psychiatric Association.¹

†In children, this criterion includes the failure to make the expected growth-related weight gains.

sive disorders (those beginning in childhood or adolescence) are at risk for bipolar disorder, particularly if they have a family history of bipolar disorder, psychotic symptoms, or a manic response to antidepressant treatment.^{2,3} Bipolar disorder is characterized by depressive episodes that alternate with periods of mania, defined by a decreased need for sleep, increased energy, grandiosity, euphoria, and an increased propensity for risk-taking behavior. Often in children and adolescents, mania and depression occur as "mixed states," in which the lability of mania is combined with depression, or there is rapid cycling between depression and mania over a period of days or even hours.⁴

Suicidal behavior is closely associated with depression. Risk factors for suicide during a depressive episode include chronic depression, coexisting substance abuse, impulsivity and aggression, a history of physical or sexual abuse, same-sex attraction and sexual activity, a personal or family history of a suicide attempt, and access to an effective means of suicide, such as a gun.^{5,6} Girls are more likely to attempt suicide, and boys to complete suicide. Among adolescents, the annual rate of suicide attempts requiring medical attention is 2.6 percent. Suicide is much rarer. Among 15-to-19-year-olds, the rates in 1998 were 14.6 per 100,000 in boys and 2.9 per 100,000 in girls.

Depression is present in about 1 percent of children and 5 percent of adolescents at any given time. Before puberty, boys and girls are at equal risk for depression, whereas after the onset of puberty, the rate of depres-

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sion is about twice as high in girls. Having a parent with a history of depression increases a child's risk of a depressive episode by a factor of 2 to 4.⁷ Anxiety, particularly social phobia, may be a precursor of depression.⁸ Depression is more common in persons with chronic illnesses such as diabetes and epilepsy and after stressful life events such as the loss of a friend, parent, or sibling.² Parent-child discord, abuse, and neglect increase the risk of depression. Alterations in central serotonergic and noradrenergic neurotransmission are associated with and may antedate childhood depression.² Screening instruments are available at no or minimal cost that are both sensitive and specific for depression, such as the Center for Epidemiological Studies-Depression Scale (available at <http://www.moodykids.org>) and the Mood and Feelings Questionnaire (available at <http://devepi.mc.duke.edu/mfq.html>).^{9,10}

STRATEGIES AND EVIDENCE

Evaluation

Medical illness should be ruled out in patients presenting with depression. For example, anemia, mononucleosis, hypothyroidism or hyperthyroidism, inflammatory bowel disease, and collagen vascular disease may cause symptoms that overlap with depression. Social functioning should be assessed in order to determine the intensity of treatment. Inpatient care is required if the patient is acutely suicidal, has substance dependence, or is psychotic, manic, or so functionally impaired that outpatient treatment cannot proceed effectively (Table 2). A patient's personal and family history should be evaluated to determine whether there is a history of mania, since approaches to treatment differ for bipolar and unipolar depression. Clini-

cians should also ascertain whether the patient has suicidal ideation and intent, a personal or family history of suicide attempts, and access to lethal agents such as firearms. Finally, the patient's home environment should be assessed for sources of stress, including parental depression and the presence of discord, abuse, or neglect, since these factors result in a poor outcome.¹¹⁻¹³

Treatment

Four components are key to the initiation of treatment. First, the parents and patient should receive education about depressive illness and its symptoms, causes, probable course, and treatment. A clear treatment contract, which reflects the confidentiality afforded the adolescent patient and its limits, helps to facilitate a trusting relationship among the adolescent, his or her family, and the clinician. Viewing depression as an illness like diabetes or hypertension helps families to take charge of its management, avoid placing blame, and set reasonable expectations regarding a treatment response. Second, identification and mitigation of hopelessness, especially about treatment, can be accomplished in part through education and a discussion of expectations. Hopelessness in depressed patients predicts withdrawal from treatment and suicidal behavior.^{5,11}

Third, a no-suicide contract should be established. This is an oral agreement among the patient, his or her family, and the clinician regarding the way in which suicidal thoughts and urges are to be handled. The patient agrees to contact a responsible adult and, ultimately, the clinician if he or she feels suicidal. The process of developing the no-suicide contract tests the ability of the adolescent and his or her family to solve problems and form a relationship with the treating clinician. The precipitants of previous suicidal behavior are identified, and a coping plan is agreed on by the patient and his or her parents.¹⁴ In one study, this approach reduced the number of suicide attempts among runaway youths who were at high risk for a suicide attempt, but this method has not been subjected to rigorous evaluation.¹⁴ Fourth, firearms should be secured or removed from the patient's home, because their presence is a risk factor for suicide.^{5,6}

Uncomplicated cases of adolescent depression can be managed by many primary care physicians, if they have adequate training, experience, and consultative support. However, depression that is complicated by a coexisting condition (e.g., attention-deficit-hyperactivity disorder or substance abuse), bipolarity, suicide attempts, psychosis, multiple episodes of depression, or treatment resistance is best handled by a child psychiatrist (Table 2).

Two types of clinical interventions have established efficacy — antidepressant treatment and certain forms

TABLE 2. INDICATIONS FOR PRIMARY PHYSICIAN CARE AND SPECIALTY CARE IN ADOLESCENTS WITH DEPRESSION.

Indications for primary physician care
Initial episode of depression
Recent onset of depression
Absence of coexisting conditions
Ability to make no-suicide contract
Indications for specialty physician care
Chronic, recurrent depression
Lack of response to initial course of treatment*
Coexisting substance abuse*
Recent suicide attempt, current suicidal ideation with plan, or both*
Psychosis*
Bipolar disorder*
High level of family discord
Inability of family to monitor patient's safety*

*The presence of this factor indicates the need for more urgent or more intensive care.

of psychotherapy. These two types of treatment are currently being compared in a large clinical trial funded by the National Institute of Mental Health. Available studies of apparently comparable subjects show similar rates of clinical response to either psychotherapy or medication. Therefore, either approach can be empirically justified, with a choice between medication and psychotherapy based on clinicians' and patients' preference.

Pharmacotherapy

Selective serotonin-reuptake inhibitors (SSRIs) are the most commonly used treatment for adolescent depression, because of the proven efficacy of fluoxetine, citalopram, and paroxetine in placebo-controlled trials, with a response rate of approximately 60 percent and a favorable side-effect profile.^{15,16} Tricyclic antidepressants are no longer considered first-line agents for adolescent depression, since controlled studies found them to be no better than placebo, and the risk of a fatal overdose is much greater than for SSRIs.^{17,18}

The recommended practice for children and adolescents is to start at half the usual dose of an SSRI (e.g., 10 mg of fluoxetine, citalopram, or paroxetine per day) for one week to help the patient adjust to any side effects and then increase the dose to the equivalent of 20 mg of fluoxetine for another three weeks (Table 3). The dose can be increased at intervals of no less than four weeks, since it takes at least four weeks at steady state to determine whether a given dose will be helpful.

Because children and adolescents metabolize SSRIs more rapidly than adults, they may often require doses above the equivalent of 20 mg of fluoxetine to attain a clinical response.¹⁹ In one report, 71 percent of patients who initially had no response to a 20-mg dose of fluoxetine had a response to an increased dose (40 to 60 mg), as compared with 36 percent of those who continued to receive the 20-mg dose.²⁰ Once an adequate clinical response has been achieved, treatment should be continued for at least six months to one year, to reduce the risk of relapse.²¹

The most common side effects of SSRIs are nausea, loss of appetite, and sedation (Table 3). Occasionally, SSRIs cause agitation, even difficulty sitting still. This side effect usually necessitates withdrawal of the SSRI and prescription of an alternative SSRI or another class of antidepressant.

Psychotherapy

Eight to 16 sessions of cognitive behavioral therapy (over a period of three to four months) have been shown to be more efficacious than alternative psychotherapies (i.e., family, supportive, and relaxation therapies) for adolescent depression.²²⁻²⁴ In this approach, patients learn to increase pleasurable activities, acquire

TABLE 3. PHARMACOLOGIC MANAGEMENT OF UNCOMPLICATED DEPRESSION IN ADOLESCENTS.

WEEK	APPROACH
1	Start treatment with a selective serotonin-reuptake inhibitor (fluoxetine, paroxetine, or citalopram*) at a dose of 10 mg daily.
2	In the absence of major side effects, increase the daily dose to 20 mg.†
4	If the response is inadequate, increase the daily dose to 40 to 60 mg.‡ If the response is adequate, continue treatment for at least 6 months to reduce the risk of relapse.

*These agents have all been shown to be effective in adolescent depression.

†Common side effects include gastrointestinal upset, minor weight loss, headache, agitation, hypomania or mania (in those predisposed to bipolar disorder), sedation or insomnia, sweating, vivid dreams, sexual dysfunction, and increased clotting time. Drug interactions are possible with medications metabolized by cytochrome P-450 coenzymes, especially 2D6 and 3A4.

‡If the response is inadequate after four to eight weeks or there are other indications for specialty care (Table 2), refer the patient to a child psychiatrist.

skills to improve interpersonal effectiveness, and identify and modify dysfunctional and self-defeating patterns of cognition that can lead to depressed mood. Another type of brief psychotherapy, interpersonal therapy, has been shown to be efficacious for adolescent depression in two clinical trials; in one it was compared with supportive clinical management,²⁵ and in the other patients were compared with controls on a waiting list for treatment.²⁶ In interpersonal therapy, adolescents learn to cope with interpersonal difficulties such as loss of relationships, discord, and role transitions that are often associated with depression. Psychotherapy may need to be continued on a monthly basis for an additional six months to decrease the risk of relapse.²⁷

Treatment-Resistant Depression

If a patient has no response to cognitive behavioral therapy or interpersonal therapy after six to eight weeks, accepted guidelines recommend adding an SSRI to the treatment regimen. Conversely, if a patient has no response to an SSRI, then adding cognitive behavioral therapy or interpersonal therapy is also supported by the literature on empirical treatment in adults. Although it is logical to posit that treating parental depression and reducing parent-child discord would enhance the treatment response in depressed adolescents, this has not been proved. Patients with chronic depression (lasting more than one year) should probably receive both medication and psychotherapy.²⁸

Before concluding that a patient has had no response to an SSRI, it is vital to ensure that the dose and adherence are adequate. Switching to another SSRI will result in an acceptable clinical response about 50 percent of the time, according to open trials in adults.²⁹ Other approaches for which there is empirical support in adults are to add lithium to the regimen or to switch to an alternative antidepressant, such as venlafaxine.^{30,31}

Treatment of Coexisting Conditions

Adolescents with depression who also have attention-deficit–hyperactivity disorder may often have no response to SSRIs alone.³² An open trial suggests that bupropion, an antidepressant with dopaminergic- and noradrenergic-agonist properties, may be efficacious in treating both depression and attention-deficit–hyperactivity disorder.³³ Substance abuse often complicates mood disorder in adolescence. Treatment of patients with both depression and alcohol abuse with SSRIs is considered safe and has improved depressive symptoms and reduced alcohol and substance abuse in randomized clinical trials of adults and in open-label studies in adolescents.³⁴ However, some of these adolescents may require specialized treatment for substance abuse.

Treatment of Bipolar Depression

Because of the relatively high risk of bipolar disorder in patients with early-onset depression, patients and their families should be taught to identify the symptoms of mania and the importance of quickly contacting the treating clinician if these symptoms emerge. Treatment of bipolar disorder is beyond the scope of this review, but it would necessitate decreasing or stopping the antidepressant medication and initiating treatment with a mood stabilizer, such as lithium or divalproex. In adults, bupropion may be less likely than other antidepressants to result in mania.³⁵

Psychotic Depression

Psychosis has been reported in up to 30 percent of patients with childhood-onset depression and is often a harbinger of bipolar disorder.^{2,3} On the basis of studies in adults, it is recommended that adolescent patients with psychotic depression be treated with a combination of neuroleptic agents and antidepressants.

Limiting Access to Lethal Agents

Families of depressed and suicidal patients should be warned about the risks of having guns in the home and should be asked to remove them. However, most families will not comply with this request when asked.³⁶ Compliance may be improved by communicating directly with the gun owner and suggesting a range of options, from securing the gun to removing it.

Fortunately, overdoses of SSRIs are rarely toxic.

However, overdoses of other medications, such as lithium, can be fatal, and access to these medications should be restricted and regulated by the patient's parents.

AREAS OF UNCERTAINTY

Areas of uncertainty in the management of adolescent depression include specific indications for antidepressant medication and psychotherapy, alone or in combination; the optimal duration of continuation and maintenance treatment, management of treatment-resistant depression, bipolar depression, depression in combination with attention-deficit–hyperactivity disorder, or substance abuse and psychotic depression; and the optimal approach to convincing families to secure or remove firearms.

Because most clinical trials of depression in adults have excluded suicidal patients, the optimal approach to the treatment of these patients remains unclear. Interventions that may reduce the risk of suicidal behavior include brief psychotherapy that targets difficulties with anger, hopelessness, and interpersonal skills — problems that often contribute to suicidal behavior in adolescents.³⁷

GUIDELINES

The American Academy of Child and Adolescent Psychiatry has published practice guidelines for handling depression and suicidal behavior in children and adolescents (available at <http://www.aacap.org>) that are reflected in our recommendations.^{6,38} Algorithms for dealing with depression in combination with other disorders and treatment-resistant depression have also been published, but they still need rigorous evaluation.^{38,39}

CONCLUSIONS AND RECOMMENDATIONS

Adolescent depression is a chronic, recurrent, and serious illness associated with substantial morbidity and mortality. It is also an eminently treatable condition that responds to SSRIs and specific psychotherapies (cognitive behavioral therapy and interpersonal therapy). For an adolescent like the boy described in the vignette, who has worsening chronic depression, a combination of medication and psychotherapy may provide the best chance for complete recovery.

Optimal treatment with SSRIs requires the use of an adequate dose, and the dose may need to be higher than that used in adults. If the adolescent in the vignette had no response to the usual dose of an SSRI in four weeks despite good compliance, we would increase the dose before considering the agent to be ineffective. If treatment with an SSRI is effective, it should be continued for at least six months after the occurrence of symptomatic relief to reduce the risk of relapse.

It is important to determine whether a patient can comply with a no-suicide contract and to encourage his or her parents to remove any firearms from the home. Patient and family education is critical. An important goal of education is to minimize the patient's feelings of hopelessness, since hopeless patients are more likely to stop treatment and to attempt suicide. Long-term follow-up is critical to identify and treat relapse if it occurs.

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