REVIEW ARTICLE

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Depression in Adolescents

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Depression is a major source of impairment and suffering in adolescence and is considered to be an important remediable risk factor for suicide, the second leading cause of death among adolescents in the United States.[1] Depression in adolescence predicts depression and anxiety in adulthood, and most affected adults had their first depressive episode during adolescence,[2] highlighting the need for early identification and treatment.

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Epidemiologic Features

Although the prevalence of depression has increased across all age groups, the increase among adolescents has outpaced that among adults.[3] The lifetime prevalence of major depressive disorder among 13- to 18-year-olds is 11.0% in the United States, with a 12-month prevalence of 7.5%.[4] Adolescent girls have both higher overall rates and more severe episodes of depression than their male counterparts; similarly, older adolescents have higher prevalence rates and more severe episodes than younger adolescents.[4] With a typical episode lasting approximately 27 weeks,[4] depression in adolescents can impair academic advancement and the attainment of important developmental milestones, such as healthy autonomy and independence.

Because depression is strongly associated with suicide, increasing rates of depression among adolescents are especially worrisome, given that rates of youth suicide have also been increasing for well over a decade.[5] Although rates of suicide have increased among both sexes, rates among girls have increased disproportionately, with the ratio of male to female suicides among 10- to 19-year-olds declining since 2007, most likely because girls have increasingly chosen lethal means, such as hanging and suffocation.[6]

Depression can be familial, and the risk of depressive disorders extends across generations. In a multigenerational study, children with depressed parents and depressed grandparents had the highest rates of major depressive disorder.[7] There is also evidence that parental depression negatively influences a young person s response to treatment for anxiety and depression,[8] and successful treatment of maternal depression is associated with a reduction in depression and improved functioning among young offspring.[9] Accordingly, identifying and treating parental depression has the potential to improve outcomes for depressed youth.

Timely recognition of and intervention for depression in adolescents has been considered a public health challenge. Risk factors for adolescent depression include female sex, family history of depression, personal history of trauma, chronic medical illness, family conflict, and minority sexual orientation.[10] The American Academy of Pediatrics, in its Guidelines for Adolescent Depression in Primary Care (GLAD-PC), lays out a framework for identification and management of depression

in adolescents, including annual universal screening for depression in children 12 to 18 years of age with the use of a validated measure, such as the Patient Health Questionnaire-9 (PHQ-9).[11]

CLINICAL PRESENTATION

Major depressive disorder is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), as depressed mood or loss of interest or pleasure for at least 2 weeks, with the primary symptom accompanied by at least four of the following additional symptoms: changes in sleep (insomnia or hypersomnia), changes in appetite or weight (decreased or increased), poor concentration or indecision, fatigue or low energy, psychomotor slowing or agitation, feelings of worthlessness or inappropriate guilt, and recurrent thoughts of death or suicide.[12] Although the DSM-5 allows irritability to be considered a symptom of depressed mood in youth, irritability in the absence of subjective dysphoria is unusual in pediatric major depressive disorder.[13] Anxiety often precedes, and is commonly present with, depression in adolescents.

Evaluation of the depressed adolescent includes an assessment for other signs and symptoms of psychopathology, particularly anxiety, mania, and psychosis. Some adolescents with major depressive disorder subsequently meet the criteria for bipolar disorder, and risk factors for bipolar disorder include an early onset of depression, depression with psychotic features, and a family history of bipolar disorder.[14] Inquiring about alcohol and substance use is also important in the evaluation of a depressed adolescent. Cannabis is the most commonly used illicit drug in adolescence, and its use has been associated with depression and suicidal behavior.[15] Finally, although depression in adolescents is relatively unlikely to be the direct consequence of unrecognized physical disease, clinicians should be alert to the possibility and pursue an evaluation for general medical conditions such as hypothyroidism or anemia when indicated by the medical history and physical examination.

Certain profiles of depression are more common in adolescence than in adulthood. Although depressed mood is the most common symptom in adolescents and adults with major depressive disorder, changes in appetite or weight, loss of energy, and insomnia are more common in adolescents, whereas anhedonia (loss of interest) and poor concentration are more common in adults.[13] It is thus clinically important to ask adolescents about changes in sleep, energy, and appetite as part of the evaluation for depression.

TREATMENT

Once clinical evaluation has confirmed the diagnosis of depression, educating both the adolescent and family members about the symptoms, course, prognosis, and treatment of depression is essential in ensuring that the patient and family are aligned with the clinician in treatment planning. Patients and their families may be aided by understanding that depression is a treatable medical illness and that recurrence of depression is common in adolescents, particularly in the absence of ongoing treatment or if treatment is abandoned prematurely.[16] Likening depression to other common and recurrent pediatric medical illnesses, such as asthma, can reduce the stigma of the disorder for the family and patient. An awareness of cultural influences on how mental health treatment may be perceived can be useful when clinicians discuss adolescent depression with families.

Beyond encouraging the basics of mood hygiene, such as a regular daily schedule, good nutrition, and moderate levels of activity and exercise, pharmacologic intervention and psychotherapy are the mainstays of treatment for depression in adolescents. The GLAD-PC recommends training for primary care clinicians who treat depression in adolescents, as well as the application of an integrated care model for providing care in the pediatric clinic rather than exclusively referring patients to specialty mental health care.[11,17] Interventions for depression that are delivered in pediatric medical settings in consultation with mental health specialists[17] and on-site brief behavioral therapy have been shown to be effective.[18] Although there has been a limited number of studies of collaborative care for depression in the pediatric population, we consider this approach to have potential for improving access to evidence-based care for depression in youth.

PHARMACOLOGIC TREATMENT

The selective serotonin-reuptake inhibitors (SSRIs) fluoxetine and escitalopram are approved

by the Food and Drug Administration (FDA) for the treatment of depression in adolescents, but other SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, are commonly used off label for this purpose. Since antidepressants can take 6 to 8 weeks to reach their maximum effect, discussing treatment expectations with adolescents and their parents assists in ensuring adherence. Once depressive symptoms have remitted, practice guidelines suggest that treatment with antidepressant medication should be continued for a minimum of 6 months, with most practitioners recommending at least a year, in order to decrease the likelihood of recurrence.[19] Because some adolescents and families are tempted to discontinue medication once the depressive episode resolves, ongoing education about the benefits of continued treatment, the risk of recurrence, and the importance of regular follow-up is critical.

Common side effects of antidepressant medications include headache, gastrointestinal discomfort, sedation or insomnia, and dry mouth. Activation, a side effect that is more common in adolescence than in adulthood, can be manifested as insomnia, disinhibition, or restlessness and may lead to discontinuation of the medication. Since these symptoms are more likely to occur with higher rather than lower starting doses of antidepressant medications or with rapid dose escalation, starting with a low dose and increasing the dose slowly can prevent or minimize activation, as well as other adverse effects.

Although most adverse effects of antidepressant treatment in adolescents are minor, patients and families should be informed about the low risk of new suicidal thinking or behavior when treatment is initiated or the dose of medication is increased, as well as the small risk of antidepressant-induced mania or hypomania. In 2004, the FDA added a black-box warning that antidepressants may increase the risk of suicidal thinking and behavior in youth. A subsequent meta-analysis of data from trials of antidepressant treatment in adolescents, which included more treatment trials than were included in the FDA analysis, showed a small but still significant risk difference of 0.7 percentage points (95% confidence interval, 0.1 to 1.3) for suicidal ideation or attempted suicide between adolescents receiving a drug and those receiving placebo.[20] Data from more recent trials of antidepressant treatment in the pediatric population show no significant difference in suicide risk between adolescents receiving placebo and those receiving antidepressant medication, possibly because these trials included suicide-specific measures, whereas the previous trials relied on reported adverse events.[21]

Antidepressants have been shown in trials to be effective for treating depression in adolescents, with a meta-analysis suggesting that the number needed to treat for 1 youth to have a response is 10.[20] The landmark Treatment for Adolescents with Depression Study showed that fluoxetine was significantly superior to placebo (response rate, 61% vs. 35%) at week 12 of treatment.[22] Though trials of antidepressants involving pediatric patients with depression typically show a high response rate with placebo, analysis has shown that higher response rates with placebo are associated with a larger number of trial sites and less severe baseline depression in study participants,[23] which suggests that improved screening of participants and a limited number of trial sites may reduce variability and improve study rigor. Response rates for placebo in federally funded studies tend to be lower than the rates in industry-funded studies.[24]

The consensus in the field of adolescent depression has been to start treatment with an SSRI at a low dose, with a subsequent increase to a therapeutic dose, and to continue treatment for 6 to 8 weeks before assessing the response to the medication (full or partial response or no response).[25] If there is a partial response, adding a second medication from a different class is a common strategy, though there are limited data on the efficacy of this approach in the pediatric population.[25] Agents typically added to a conventional antidepressant are bupropion, lithium, and atypical antipsychotic medications.

The most extensively studied strategy for the approximately 40% of adolescents who do not have a response to an initial antidepressant trial is to switch to another SSRI rather than add another medication, an approach based on results from the Treatment of Resistant Depression in Adolescents study.[26] In this trial, adolescents who were switched to a different SSRI were as likely to have a reduction in depressive symptoms as those treated with the SNRI venlafaxine, and the venlafaxine group had more side

effects. Moreover, participants who received both antidepressant medication and cognitive behavioral therapy (CBT) had significantly greater improvement than those who received medication without CBT.[26]

PSYCHOTHERAPY

CBT and interpersonal psychotherapy (IPT) have been shown to be effective in treating depression in adolescents.[27] CBT focuses on the role of thoughts, feelings, and behaviors and their interactive effect in maintaining or reducing depression. Adolescents are taught to identify negative thoughts and reframe them as realistic thoughts, weighing the evidence that supports or negates them. IPT, which focuses on the relationship between depression and interpersonal interactions, reduces depressive symptoms while improving functioning by teaching patients to recognize their emotions and by working to improve interpersonal communication and problem-solving skills. A review of randomized, controlled trials of psychotherapy as compared with placebo or other active treatments showed the efficacy of CBT and IPT across independent research groups.[27]

Predictors of a poor response to psychotherapy across studies have included severe depression, low global functioning on assessment, high scores on suicidality measures, coexisting anxiety, distorted thought patterns, feelings of hopelessness, and family conflict.[27] Anxiety reduced the treatment response but did so less prominently for CBT than for IPT. CBT was less effective than IPT in adolescents with substantial life stress, particularly family conflict. Likewise, IPT was better than CBT for adolescents with parental conflict and challenging peer relationships.[27]

FUTURE DIRECTIONS

Areas currently being investigated that have the potential to improve the treatment of depression in adolescents include pharmacogenetics, diet and nutrition, and treatment that is individualized on the basis of extensive personal and clinical data.[28-30] As with depression in adults, there is interest in studying treatments that can rapidly ameliorate depression and suicidality in adolescents, such as ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and its analogues. Transcranial magnetic stimulation, a neuromodulatory treatment, is approved in adults with depression who have not had a response to at least one antidepressant trial and is currently under investigation for the treatment of adolescents with depression.

Psychotherapy and antidepressant medication are effective in treating depression in adolescents. However, earlier identification and treatment, attention to the need for treatment of parental depression, and the development of new therapeutics for adolescents who do not have a response to current treatments would be beneficial.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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