# An Update on Depression in Children and Adolescents

*This ACADEMIC HIGHLIGHTS section of* The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "Advances in the Treatment of Depression in Children and Adolescents," which was held in May and June 2008. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Forest Pharmaceuticals, Inc.*

*The planning teleconference series was chaired by* ***Karen D. Wagner****, M.D., Ph.D., Department of Psychiatry and Behavioral Sciences, and the Division of Child and Adolescent Psychiatry, University of Texas Medical Branch, Galveston. The faculty were* ***Graham J. Emslie****, M.D., Department of Psychiatry and Pediatrics, University of Texas Southwestern Medical Center, and the Division of Child and Adolescent Psychiatry, Dallas;* ***Robert A. Kowatch****, M.D., Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; and* ***Elizabeth B. Weller****, M.D., Department of Child and Adolescent Psychiatry, Children's Hospital of Philadelphia, Philadelphia, Pa.*

*Financial disclosure:* ***Dr. Wagner*** *receives research support from the National Institute of Mental Health (NIMH) and is a consultant for or a member of the advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, Johnson & Johnson, Otsuka, Solvay, and Wyeth.* ***Dr. Emslie*** *has received research support from NIMH, Biobehavioral Diagnostics, Forest, Shire, and Somerset and is a consultant for Biobehavioral Diagnostics, Eli Lilly, Forest, Shire, and Wyeth-Ayerst.* ***Dr. Kowatch*** *has received research support from Bristol-Myers Squibb, the Stanley Research Foundation, NIMH, and the National Institute of Child Health and Human Development; is a consultant for or a member of the advisory boards for the Child Adolescent Bipolar Foundation, Abbott, Sanofi-Aventis, GlaxoSmithKline, and Medscape; is an editor for Current Psychiatry; and is a member of the speaker's bureau for AstraZeneca.* ***Dr. Weller*** *has received grant/research support from NIMH, Otsuka, GlaxoSmithKline, Wyeth-Ayerst, Forest, and AstraZeneca; has received royalties from American Psychiatric Press Incorporated (APPI Press); and is an emeritus director of the American Board of Psychiatry and Neurology.*

*Dr. Weller acknowledges Abigail Dubin-Rhodin for editorial assistance.*

*The opinions expressed herein are those of the faculty and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.*



According to the National Alliance on Mental Illness, at any one time, about 2% of school-aged children and 4% of adolescents appear to experience depression.[1] Pediatric depression often results in physical, emotional, and social impairment, which may persist into adulthood. Recognition and effective treatment of pediatric depression may improve long-term outcomes, but only a minority of youths who meet the criteria for this disorder are diagnosed and treated.[2]

In this ACADEMIC HIGHLIGHTS, Elizabeth B. Weller, M.D., described the epidemiology, risk factors, and diagnosis of depression in youths. Robert A. Kowatch, M.D., Ph.D., examined the epidemiology of suicide in youths, factors that may lead to suicide, and the possible association of antidepressant medications with suicide. Karen D. Wagner, M.D., Ph.D., discussed the efficacy of antidepressant medications, psychotherapies, and their combination for the treatment of youths with depression. The course of pediatric depression, strategies for resolving treatment-resistant depression, and continuation and maintenance treatment were addressed by Graham J. Emslie, M.D.

## Diagnosing Childhood and Adolescent Depression

Although case reports of depression in children and adolescents date back to the 17th century, explained Dr. Weller, the existence of depression in young people was not recognized in the United States until 1975.[3] Since then, the diagnosis of depression in youths has received more attention.

### Schools of Thought

In the past 30 years, different schools of thought have surrounded depression in children and adolescents. Some people believed that youths do not experience depression because children lack a sufficiently developed superego and do not have adult concerns such as bills to pay. Others suggested that youths experience "masked" depression, which is revealed through behavioral problems, and that depression in youths has features not present in adults, such as additional somatic complaints.[4] Finally, in 2000, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[5] stated that depression can be diagnosed in children and adolescents and that the same criteria used for adults are appropriate.

### Epidemiology

During the 20th century, depression rates in the United States progressively increased and age at onset became steadily younger.[6] Currently, around 1% of preschoolers, 2% of school-aged children, and as many as 8% of adolescents have depression.[7] After puberty, rates of depression are higher in females.[8] According to Dr. Weller, prepubertal major depressive disorder (MDD) tends to predict MDD during adolescence but not necessarily during adulthood.[9]

Childhood MDD tends to feature mood reactivity, irritability, dysphoria, and comorbidity with disruptive disorders.[9] Adolescent MDD is chronic and recurrent, shares features of MDD at older ages, is associated with functional impairment, and has high comorbidity with anxiety, substance use disorders, and suicidal behavior.[9]

### Risk Factors

Dr. Weller stated that risk factors for childhood and adolescent depression include individual characteristics, stressful events or situations, interpersonal problems, and other factors (Table 1).

***Stressors specific to adolescents***. Certain changes occur during adolescence, explained Dr. Weller, that put youths at high risk for depression. Roles and expectations change between childhood and adolescence, and physical, intellectual, and hormonal changes occur. Stressors that are faced by adolescents include forming an identity, dealing with their emerging sexuality, separating from parents, and making decisions for the first time.[10]

Female high school students have significantly higher rates of depression than male students.[10] A biological explanation for higher rates of depression among girls may be the increase in the hormone oxytocin during puberty, which leads to an increase in affiliative behavior and a need for emotional connectivity; as a result, when an emotional bond with a loved one is broken, the girl may experience a sense of loss leading to depression.[11] Girls also may have a greater number of stressful experiences during adolescence than boys and react more strongly to these experiences.[12] External pressures that may lead to depression in adolescent females include society's expectations about proper behavior for women[13] and stereotypical ideals of an extremely thin physical appearance.[14]

### Diagnostic Process for Childhood and Adolescent Depression

The DSM-IV-TR[5] criteria for adults should be applied to the diagnosis of childhood and adolescent depression. Specific categories of symptoms should be considered (Table 2).[15]

***Differential diagnosis***. Dr. Weller explained that the diagnosis of MDD in children and adolescents involves focusing on the presentation and remembering that comorbidities often exist. Children and adolescents may have comorbid attention-deficit/hyperactivity disorder, conduct disorder, learning disability, anxiety disorders, eating disorders, or substance use disorders.

Other conditions may easily be mistaken for depression, so clinicians should be exceptionally careful in the differential diagnosis. Depression should be distinguished from an adjustment disorder with depressed mood, which may not require aggressive treatment with antidepressants. Also, grief often presents with depressive symptoms and should be separated from MDD. Dr. Weller added that children with learning disabilities who feel demoralized and those with medical conditions who are apathetic should not be mistakenly diagnosed with MDD.

Dr. Weller clarified the differences between depression and dysthymia.[5] Specifically, symptoms of MDD are severe and present daily for 2 weeks or more, psychosis exists, and impaired functioning is common. Symptoms of dysthymia are mild to moderate and fluctuate on and off for approximately 1 year, no psychosis exists, and impaired functioning is rare.

***Data collection***. Dr. Weller recommended that the diagnostic process for childhood and adolescent depression incorporate the life-line approach—partnering with the patient and the family to understand the patient's developmental trajectory.[16] In this process, structured interviews should be used and a 3-generational family history of psychiatric and medical disorders should be taken.

Throughout the diagnostic process, clinicians should pay attention to verbalization by the child. Information from the mother, father, caretaker, or teacher should be collected; however, the clinician should judge the informant's accuracy. A parent who is also depressed may overreport the child's depressive behavior, since he or she is likely sensitive to the issue. Conversely, a depressed parent may underreport depressive symptoms and attribute the child's behavior to a conduct disorder because of differing symptomatology between adult and childhood MDD; the parent feels melancholic whereas the child's depression is irritable.

Further information that should be collected by the clinician includes: (1) the chief complaint of the child and the parents; (2) the reason for referral; (3) the history of the present illness, i.e., age at onset and the duration, frequency, and intensity of symptoms, remissions, and relapses; (4) the effects of the symptoms on the child and family; and (5) precipitating events. Dr. Weller added that the prognosis is usually better if precipitating events occurred because the end of these events may help the depression subside.

Clinicians should record the complete history of the youth's social, emotional, and behavioral problems from preschool to the current grade, as well as interventions that were sought and whether the interventions were helpful. In addition, the youth's mental status should be thoroughly examined; during this examination, specific factors should be documented (Table 3).

**FOR CLINICAL USE**

- Screen children and adolescents for mood disorders, especially in the presence of poor school performance, substance abuse, poor social skills, and social withdrawal. If depressive symptoms are apparent, ask about current thoughts of death or dying, specific suicide plan, or past suicide attempts.
- Individualize treatment with pharmacotherapy combined with cognitive-behavioral therapy or interpersonal psychotherapy.
- Continue maintenance treatment for at least 1 year in patients who took a long time to remit or had psychosis, comorbidity, suicidality, family disruption or psychopathology, or who lack community support.




© COPYRIGHT 2008 PHYSICIANS POSTGRADUATE PRESS, INC.

***Diagnostic tools***. Dr. Weller stated that the careful use of diagnostic tools such as structured interviews and rating scales can facilitate an accurate diagnosis of depression in children and adolescents. The possibility of using biological tests was also discussed.

*Interviews*. Both structured and semistructured interviews are available for assessing psychiatric disorders in children and adolescents. The Diagnostic Interview for Children and Adolescents,[17] the Diagnostic Interview Schedule for Children, Version 2.3,[18] and the Children's Interview for Psychiatric Symptoms (ChIPS)[19] are structured interviews that have both child and parent components. The ChIPS can be completed in 1 hour or less. The Schedule for Affective Disorders and Schizophrenia for School-Age Children,[20] another semistructured interview with child and parent components, is extremely detailed and usually takes about 3 hours to complete; thus, clinical experience is needed to conduct this interview.

*Rating scales*. Several self-rated and clinician-rated scales were discussed by Dr. Weller. Each scale was created for a specific age group.

The Berkeley Puppet Interview[21] is a novel self-report rating scale that was created for preschoolers. The Children's Depression Inventory–Short Form,[22] a 10-item, self-rated questionnaire, was created for children aged 7 to 17 years and is comparable to the original 27-item Children's Depression Inventory.[23] Children lose interest and get impatient, so shorter scales are better as long as they are reliable, said Dr. Weller.

The Beck Depression Inventory for Youth (BDI-Y)[24] is a 20-item, self-report questionnaire for children aged 7 to 14 years. The BDI-Y is written at a second-grade reading level and takes 5 to 10 minutes to complete. Items from the following 5 domains are included: negative views of the self, negative views of the world, and motivational, physiological, and emotional symptoms of depression. This information about hallmark symptoms of depression is useful for cognitive therapy providers, commented Dr. Weller.

The Reynold's Adolescent Depression Scale[25] is a 30-item scale that determines the severity of depression in 13- to 18-year-olds. The scale can be used in school or clinical settings and assesses the frequency of the following 4 domains of depression in adolescents: dysphoric mood, anhedonia/negative affect, negative self-evaluation, and somatic complaints.

According to Dr. Weller, the Children's Depression Rating Scale Revised (CDRS-R)[26] is likely the most useful scale and is for children and adolescents aged 7 to 18 years. The 17-item, observer-rated instrument measures the severity of depressive symptoms and takes about 30 minutes to complete.

Dr. Weller also recommended using the Young Mania Rating Scale (YMRS),[27] an 11-item instrument, to determine the severity of the patient's condition during the past week. The YMRS is both self-rated and observer-rated and takes about 15 to 30 minutes to complete. Dr. Weller suggested the use of this scale because identifying any present mania symptoms may predict bipolar disorder in the future.

**Table 1. Risk Factors for Childhood and Adolescent Depression**

| Type | Risk Factors |
|---|---|
| Individual | Being female and having a prior history of depression, subclinical depressive symptoms, a neurotic personality, and negative cognitions |
| Interpersonal | Family issues such as conflict and a lack of attachment/bonding, warmth/acceptance, and control/autonomy; peer problems such as rejection; and trouble with romantic relationships |
| Stress | Abuse or maltreatment, family violence, poverty or chronic financial strain, loss and separations, failure, disappointments, and familial depression |
| Other | Medical conditions, psychiatric conditions such as anxiety and disruptive disorders, and alcohol or drug abuse |

**Table 2. Some Symptoms of Depression to Note in Children and Adolescents[a]**

| Type | Symptoms |
|---|---|
| Affective | Anxiety, anhedonia, melancholia, depressed or sad mood, irritable or cranky mood |
| Motivational | Loss of interest in daily activities, feelings of hopelessness and helplessness, suicidal thoughts, suicidal acts or attempts |
| Cognitive | Difficulty concentrating, feelings of worthlessness, sense of guilt, low self-esteem, negative self-image, delusions or psychosis |

[a]Adapted with permission from Waldinger.[15]

**Table 3. Factors to Consider When Examining the Mental Status of Children and Adolescents**

| |
|---|
| Physical appearance and grooming |
| Interactions with the clinician |
| Motor activity level |
| Attention level |
| Mood and affect |
| Anxiety |
| Persistence |
| Frustration |
| Tolerance |
| Impulsivity |
| Oppositionality |
| Verbal/physical aggression |
| Speech and language |
| Hallucinations/delusions or thought disorder |
| Clinical estimate of intelligence |
| Judgment and insight |
| Suicidal/homicidal thoughts, acts, or plans |

*Biological tests*. Dr. Weller said that brain imaging is not clinically useful at this time, although findings[28–30] in youths with MDD have included reduced frontal cortical volume[28] (associated with familial MDD), increased ventricular volume,[28] increased choline in the frontal lobe,[29] and increased serotonin in the midbrain.[30] Tests such as the dexamethasone suppression test, growth-hormone releasing hormone, and insulin challenges also are not currently used in clinical settings, stated Dr. Weller.

### Depression and Pregnancy

Some adolescents become pregnant and may be depressed before or after the pregnancy begins. Dr. Weller stated that this population has special issues for clinicians to address.

Not treating depression during pregnancy may increase health risks for both the mother and baby. The mother with untreated depression may experience relapse, substance abuse, and lower utilization of prenatal care.[31] The health risks of untreated maternal depression to the baby include low birth weight and premature birth.[31]

However, pharmacologic treatment of depression during pregnancy also presents risks, such as poor neonatal adaptation syndrome and persistent pulmonary hypotension of the newborn.[32] Dr. Weller cautioned that paroxetine should not be given to pregnant females since the risk of fetal malformation, especially cardiac defects, may be higher with this drug.[33]

On May 29, 2008, the U.S. Food and Drug Administration (FDA) proposed a new rule[34] that would require changes in the format and content of prescription drug labeling for pregnant or lactating patients. Dr. Weller advised clinicians who treat depressed adolescents to watch for changed labels for pregnancy and lactation.

### Conclusion

Children and adolescents with MDD have a high rate of recurrence. MDD often continues into adulthood and increases the risk of suicide attempts as well as psychiatric and medical hospitalizations. Poor school performance, substance abuse, poor social skills, and social withdrawal are common outcomes of untreated MDD; however, the most serious outcome is suicide.[35] For these reasons, concluded Dr. Weller, correct diagnosis and adequate treatment of young patients are of extreme importance.

## Suicide in Children and Adolescents With Depression

Dr. Kowatch explained that suicidal behavior is a common and serious complication of MDD. Around 60% of children with a depressive disorder will have suicidal ideation, and about 30% will make a suicide attempt.[35]

### Epidemiology of Suicide in Youths

In the United States, the suicide rate for adolescents and young adults has been steadily increasing since 2003.[36] In 2004, suicide was the third leading cause of death for this age group, after motor vehicle accidents and homicide.[36]

Between early adolescence and young adulthood, suicide rates increase dramatically (Figure 1).[37,38] Suicide rates continue to increase throughout adulthood.[37] The 3 most common methods of suicide among adolescents and young adults are use of firearms, hanging/suffocation, and poisoning.[36]

Although female adolescents are more likely to attempt suicide, males are more likely to complete suicide; this likelihood increases with age.[37] In addition, American Indian and Alaskan native adolescents have the highest suicide rate across all ethnic groups; the rate is nearly double that of white non-Hispanics (Figure 2).[37,38]

### Spectrum of Suicidality

Dr. Kowatch explained that suicidality in youths occurs along a continuum. Suicidal ideation is the thought of harming or killing oneself. A suicide *attempt* is a nonfatal, self-inflicted destructive act with explicit or inferred intent to die. A single attempt or multiple attempts may be made, but the prognosis is worse if multiple attempts are made. *Completed* suicide is a fatal self-inflicted act with explicit or inferred intent to die.

Dr. Kowatch clarified that not all youths first experience ideation, then make an attempt, and finally complete suicide. Some children only experience ideation; others impulsively take their own lives without thoughtful planning.

Dr. Kowatch clarified that suicidal behaviors are different from self-harm behaviors, which are performed to inflict pain but not to die. With suicidal behaviors, the intent is to die.

### Precipitants of Suicide

A youth may have multiple reasons for suicide. However, often an adolescent is on the verge of ending his or her own life and a particular psychosocial precipitant is the deciding factor, explained Dr. Kowatch. Brent et al.[39] conducted a psychological autopsy of 140 adolescent suicide completers aged 13 to 19 years. A history of abuse (lifetime or current) was the most common feature among the sample. Among those 16 years or under, the next most frequent stressors were parent-child conflict and boyfriend-girlfriend conflict. Among subjects over the age of 16 years, the most common stressors after abuse were legal/disciplinary problems and the loss of a romantic relationship. Among both age groups in the sample, the greatest risk factor for completed suicide was a mood disorder.

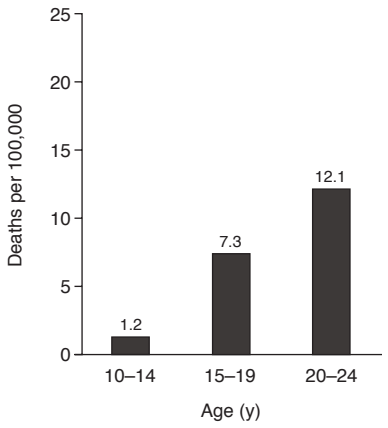
Bridge et al.[40] found that a previous suicide attempt substantially increases the risk of completing suicide (OR = 67.4, 95% CI = 16.3 to 280). Other risk factors included mood disorder, any psychiatric disorder, substance use disorder, conduct disorder, and anxiety disorders. Youth with the highest risk for completed suicide had a mood disorder and had made a previous attempt.

Dr. Kowatch described the "developmental-transactional model of youth suicidal behavior" developed by Bridge et al.,[40] emphasizing the central role of depression (Figure 3). The model was created to identify risk factors for suicidal behavior, which may aid in intervention. According to this model, genetic and environmental factors affect children at an early age and increase the likelihood of depression, suicidal behavior, and completed suicide. The development of certain traits such as impulsive aggression also is a risk factor for suicidal behavior.



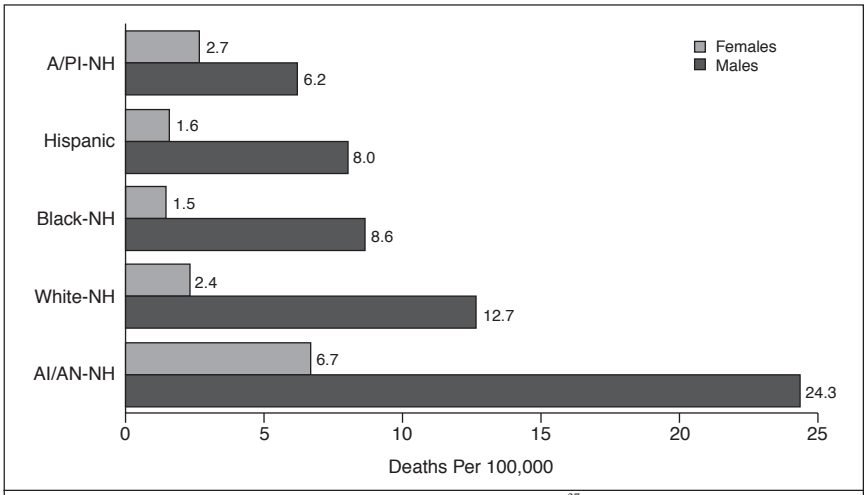

© COPYRIGHT 2008 PHYSICIANS POSTGRADUATE PRESS, INC.

**Figure 1. Suicide Rates for Adolescents and Young Adults in 2003[a]**




[a]Data from the National Adolescent Health Information Center[37] and the Centers for Disease Control and Prevention.[38]

**Figure 2. Suicide Rates by Race/Ethnicity and Gender for Adolescents and Young Adults in 2003[a]**




[a]Data from the National Adolescent Health Information Center[37] and the Centers for Disease Control and Prevention.[38]
Abbreviations: A/PI = Asian/Pacific Islander, AI/AN = American Indian/Alaskan Native, NH = non-Hispanic.

Stressors often trigger suicide attempts. Facilitators increase the likelihood of completed suicide. However, protective factors can decrease the risk of acting on suicidal ideation.

Adolescents with the highest risk of suicidal behavior are those who have a history of impulsive aggression, use drugs or alcohol, are currently depressed, and have a family history of suicide,[40] stated Dr. Kowatch. Psychosocial stressors may precipitate attempted or completed suicide among these adolescents.[40]

## Antidepressant Medications and Suicide in Youths

In 2003, the United Kingdom banned all antidepressants except fluoxetine for treatment of pediatric depression, following a meta-analysis[41] that showed an increase in suicide among adolescents taking antidepressants. Following this decision, the FDA began a series of data analyses and public hearings to examine whether or not pediatric antidepressant use was worth the risk. In October 2003, the FDA issued a public health advisory warning of attempted and completed suicides among youths while taking selective serotonin reuptake inhibitors (SSRIs).

***The "black box" warning.*** In October 2004, the FDA again issued a public health advisory warning that pediatric antidepressant use may lead to suicide and required pharmaceutical companies to include a "black box" warning on all antidepressant medications. The following year, specific wording for the warning was provided by the FDA, and pharmaceutical companies were required to provide educational information to patients.

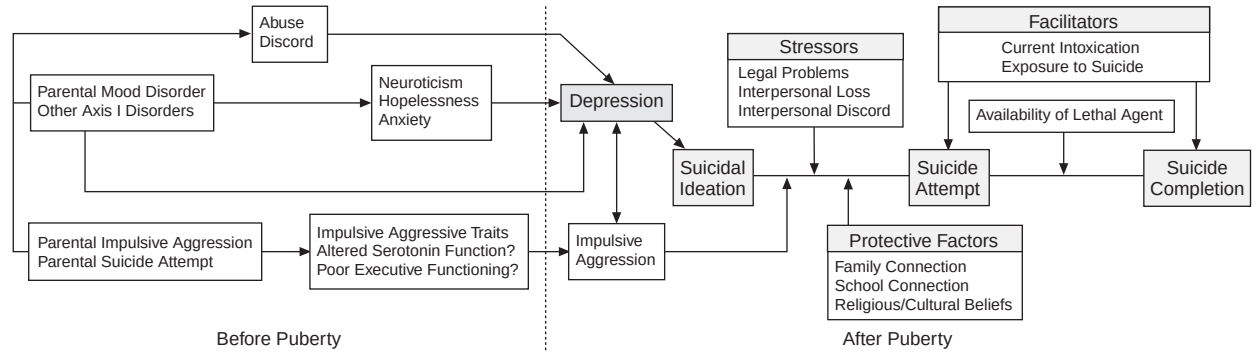
The black box warning states that antidepressants increase the risk of suicidal thinking and behavior in children and adolescents with MDD and other psychiatric disorders. When considering the use of an antidepressant, the risk should be balanced with the clinical need. Pooled analyses[42] of placebo-controlled, 4- to 6-week trials of 9 antidepressant drugs revealed a greater risk of suicidal thinking or behavior during the first few months of treatment. Although no suicides occurred, the average risk of these events with antidepressants was 4%, twice the placebo rate of 2%. Dr. Kowatch added that the suicidal events typically took place early in treatment.

Dr. Kowatch recommended that clinicians warn parents about the increased risk of suicidal ideation and behavior, discuss benefits of antidepressant use versus the risks, and be in close contact with patients during the first 4 to 6 weeks of treatment (both in person and by telephone).

***Effects of FDA advisory.*** Libby and colleagues[43] studied a pediatric database of more than 65,000 records and found that, from 1999 to 2004, the rate of newly diagnosed depression in youths steadily increased. However, in 2005, rates of observed depression decreased sharply. In addition, before the 2003 advisory, pediatricians and primary care providers diagnosed the majority of episodes of depression, but by 2005, patients were more often diagnosed by psychiatrists than primary care doctors. Also, after the 2003 advisory, the mean percentage of depressive episodes in which the patient received an SSRI decreased from 59% to 28% and those in which the patient did not receive an antidepressant prescription increased from 20% to 64% by 2005.

***Re-evaluation of antidepressants.*** In response to the FDA warnings about antidepressants, Bridge et al.[44] conducted a large meta-analysis to examine the efficacy of antidepressants and the risk of suicidal ideation and attempts in the treatment of pediatric depression. The study[44] reported that,

**Figure 3. The Developmental-Transactional Model of Youth Suicidal Behavior[a]**




[a]Adapted with permission from Bridge et al.[40]

**Table 4. Suicide Prevention Resources**

| Resource | Description | Location |
|---|---|---|
| The Columbia Health Screen | A 14-item, self-completion questionnaire that identifies risk factors of teen suicide | Columbia University TeenScreen Program www.teenscreen.org/health-professionals |
| Facts for Families: Teen Suicide | A resource that provides facts and advice for families to prevent teen suicide | American Academy of Child and Adolescent Psychiatry www.aacap.org/cs/root/facts_for_families/teen_suicide |
| American Foundation for Suicide Prevention | A nonprofit organization that strives to prevent suicide and help those who have been affected by suicide | www.afsp.org/ |
| American Association of Suicidology | A nonprofit organization that strives to understand and prevent suicide through research, public awareness, and education | www.suicidology.org/ |

among trials that included patients with MDD, pooled rates of response were 61% for antidepressant-treated patients and 50% for placebo-treated patients. The pooled rates of suicidality (ideation/attempt) were 3% in antidepressant-treated subjects and 2% in those receiving placebo; no completed suicides occurred. The number needed to treat (NNT) for SSRIs was 10, which means that for every 10 depressed youths treated with medication, 1 additional patient responded who would not have responded to placebo. An NNT of 10 indicates an overall favorable risk-to-benefit profile for antidepressants in the treatment of pediatric MDD. However, antidepressants were more effective in pediatric anxiety than depression, and, in children under 12 years old, only fluoxetine was more effective than placebo. Dr. Kowatch stated that the evidence presented in this study supports the cautious and well-monitored use of antidepressants as first-line treatment for adolescents with MDD.

The Treatment of Adolescents With Depression Study (TADS)[45] compared the efficacy and suicidality features of fluoxetine, cognitive-behavioral therapy (CBT), and combination therapy with fluoxetine and CBT in adolescents with MDD. At week 36, rates of response were 81% for fluoxetine monotherapy, 81% for CBT, and 86% for combination therapy. Suicidal ideation and behavior occurred more often with fluoxetine monotherapy (14.7%) than with CBT (6.3%) or combination therapy (8.4%) and decreased throughout treatment. Overall, explained Dr. Kowatch, the risk-to-benefit profile of fluoxetine in the treatment of pediatric MDD was favorable.

## Conclusion

Dr. Kowatch concluded by stressing the importance of screening children and adolescents for mood disorders. Clinicians should ask parents about any changes in the child or adolescent's behavior or mood, such as withdrawal from others, changes in sleep or appetite, and changes in academic performance. If significant depressive symptoms are apparent, the youth should be asked about current thoughts of death or dying, specific suicide plans, or past attempts.

Dr. Kowatch added that clinicians should evaluate the risk factors for possible suicide, including older age, male sex, current stressors, family history of mood disorders or suicide, and comorbid disorders (e.g., ADHD, substance abuse). Feelings of hopelessness and a history of impulsivity should also be examined. In addition, access to firearms should be evaluated. If the youth is significantly depressed or experiencing suicidal ideation, then any firearms should be removed from the home.

Dr. Kowatch recommended that clinicians use resources to help them uncover and resolve suicidality. Several screening questionnaires exist, as well as suicide prevention resources (Table 4).




© COPYRIGHT 2008 PHYSICIANS POSTGRADUATE PRESS, INC.

## Acute Treatments for Pediatric Depression

Dr. Wagner stated that major treatment modalities for pediatric depression include pharmacotherapy and psychotherapy as well as family involvement in the treatment plan.

### Pharmacotherapy

Only 1 medication—fluoxetine—has been approved by the FDA for the treatment of major depression in children and adolescents, aged 8 to 17 years. The superiority of fluoxetine to placebo in the treatment of youths with major depression has been demonstrated in 3 double-blind trials.[46–48]

Other SSRIs that have demonstrated efficacy for treatment of pediatric depression include citalopram, sertraline, and escitalopram (for adolescents). An 8-week controlled study[49] of children and adolescents with major depression reported statistically significantly greater improvement in CDRS-R scores throughout the study in citalopram-treated patients compared with placebo-treated patients. An a priori pooled analysis[50] of two 10-week controlled trials of sertraline in children and adolescents with major depression observed significantly greater improvement in CDRS-R scores from baseline to endpoint for patients treated with sertraline compared with those treated with placebo ($p = .007$). Recently, an 8-week controlled trial[51] of escitalopram in adolescents with major depression reported significant improvement in CDRS-R scores in escitalopram-treated patients compared with placebo-treated patients ($p = .022$).

Dr. Wagner stated that SSRIs can be considered first-line medication for children and adolescents with MDD.[52] However, patients taking SSRIs should be carefully monitored.

Some antidepressants that are commonly used in clinical practice have failed to demonstrate efficacy in acute treatment trials. Medications that have failed to demonstrate statistically significant superiority to placebo on primary efficacy measures in pediatric depression studies include paroxetine,[53–55] escitalopram,[56] mirtazapine,[57] nefazodone,[58] citalopram (for adolescents),[59] and venlafaxine.[60] Methodological issues such as site selection, patient recruitment strategy, inclusion-exclusion criteria, small sample size, study design, and outcome measures chosen may have contributed to some trials' negative outcomes.[61] Of particular note, placebo response rates were high in these trials (Table 5). According to Dr. Wagner, more information about the overall efficacy of antidepressants for the acute treatment of children and adolescents with MDD is needed. However, the TADS trial[45] suggested that response to pharmacotherapy improves over time; fluoxetine response rates increased from 62% at 12 weeks to 69% at 18 weeks and 81% at 36 weeks.

**Table 5. Positive and Negative Studies of Antidepressants in Child and Adolescent Depression[a]**

| |
|---|
| Positive Studies[a] |
| Fluoxetine[46–48] |
| Citalopram[49] |
| Sertraline[50] |
| Escitalopram (adolescents)[51] |
| Negative Studies[b] |
| Paroxetine[53–55] |
| Escitalopram[56] |
| Mirtazapine[57] |
| Nefazodone[58] |
| Citalopram (adolescents)[59] |
| Venlafaxine[60] |

[a]Positive studies indicate a statistically significant difference with the medication vs. placebo.
[b]Negative studies indicate the medication failed to demonstrate statistically significant superiority over placebo.

### Psychotherapy

Dr. Wagner stated that CBT and interpersonal psychotherapy for adolescents (IPT-A) are the most studied psychotherapies for adolescents with depression. The focus of CBT is on cognitive distortions and behavioral deficits in youths with depression.[62] Components of treatment with CBT include psychoeducation, mood monitoring, pleasant activity scheduling, and cognitive restructuring. The focus of IPT-A is on features of interpersonal relationships related to depression, including loss, disputes, role transition, and interpersonal deficits. Developmental issues such as separation from parents, reaction to authority figures, peer pressures, and dyadic relationships have been added for treatment of adolescents.[63]

***Efficacy of CBT***. In a 12- to 16-week comparison of CBT, systemic behavior family therapy, and nondirective supportive therapy, CBT resulted in greater reduction in depression, faster symptom relief, and higher remission rates than the other 2 treatments.[64] Rohde and colleagues[65] reported posttreatment improvement in depression and social functioning following a cognitive-behavioral group intervention compared with a life skills/tutoring control group in adolescents with comorbid major depression and conduct disorder, although at 6- and 12-month follow-up, no significant differences between groups remained. In the TADS trial,[48] involving adolescents with MDD, CBT was not significantly more effective than placebo by week 12. However, when the same cohort continued treatment for 36 weeks, CBT became as effective as fluoxetine.

***Efficacy of IPT-A***. The efficacy of IPT-A for clinic-referred adolescents with depression was assessed in a 12-week randomized trial.[66] Greater reduction in depressive symptoms and improved social functioning were found in the IPT-A group compared with a clinical monitoring group. In school-based clinics, adolescents with major depression who received IPT-A had greater symptom reduction and improved functioning compared with those who received treatment as usual.[67]

***Meta-analyses.*** Two recent meta-analyses[68,69] have assessed the effectiveness of psychotherapy for the treatment of depression in children and adolescents. One meta-analysis[68] included all studies with random assignment to an active treatment and a nontreatment control for subjects with

MDD and dysthymia; this review found that the effect size of psychotherapy for the treatment of depressed youths was modest (effect size = .34). Moreover, cognitive therapy such as CBT was not superior to noncognitive therapies. The review also found a short-term but not long-term effect of psychotherapy. In another meta-analysis[69] of 27 randomized, controlled trials of depression in children and adolescents, psychotherapy was found to be effective at posttreatment, but, at 6-month follow-up, the effectiveness of psychotherapy was no longer significant. Dr. Wagner asserted that these results suggest that lengthening psychotherapy treatment for depressed youths beyond 12 to 16 weeks is needed to maintain effectiveness.

### Combination Pharmacotherapy and Psychotherapy

Does added benefit exist for combination treatments compared with pharmacotherapy alone or psychotherapy alone in the treatment of pediatric depression? Dr. Wagner said that this question was addressed in the TADS,[48] which is the largest randomized, controlled trial for adolescents with major depression. After the first 12 weeks of treatment, remission rates were statistically significantly higher in the fluoxetine-plus-CBT group (37%) compared with the fluoxetine monotherapy (23%), CBT (16%), and placebo (17%) groups.[70] However, added Dr. Wagner, these remission rates were all low. Combination treatment resulted in greater improvement in functioning and quality of life in depressed adolescents than fluoxetine monotherapy, and CBT alone had no significant differences from placebo on functioning and quality-of-life measures.[71] Predictors of acute response to any treatments were younger age, less hopelessness with less suicidal ideation, less chronic depression, better functioning, fewer comorbid disorders, and greater expectation for improvement.[72]

Dr. Wagner explained that, although the TADS[48] found an advantage for combination treatment, other studies have not shown this added benefit. For example, one 12-week trial[73] randomly assigned 208 adolescents with MDD to either treatment with an SSRI and routine care or treatment with an SSRI, routine care, and CBT; no difference in outcome was found between treatment groups. Similarly, in a 12-week, randomized trial[74] of treatment with CBT, sertraline, or the combination in depressed adolescents, all groups showed improvement in depressive symptoms. Combination treatment was not more effective than either treatment alone. Finally, a 28-week cost-effectiveness study[75] concluded that the combination of CBT and an SSRI was not more cost-effective than an SSRI alone for treating adolescents with depression in routine clinical care.

### Conclusion

Dr. Wagner concluded that depressed children and adolescents may benefit most from individualized treatments for depression. Future clinical research should be aimed at identifying effective treatment based upon the individual characteristics of each depressed child.

## Long-Term Outcomes of Pediatric Depression

Pediatric depression is frequently a chronic and recurrent condition that lasts for many years and often into adulthood. Long-term consequences of the illness can include school and work-related problems, substance abuse, suicide attempts, and legal difficulties, stated Dr. Emslie.

### Naturalistic Course

Dr. Emslie explained that most patients experience remission from depression within 1 to 2 years; however, relapse and recurrence rates are high.[76] Early-onset depression often leads to adult MDD. Predictors of relapse and recurrence appear to include prior episodes, severe depression, suicidality, residual symptoms after acute treatment, and family history.

***Treatment stages***. Because terminology for stages of treatment are often inconsistent, Dr. Emslie clarified these terms. Specifically, treatment of depression can be divided into 3 stages—acute, continuation, and maintenance treatment.[77]

The initial goal for the acute phase is achieving response to medication; however, the ultimate goal is remission, so that at the end of the acute phase, the patient would have few or no symptoms. When patients have no response or partial response to acute treatment, they may have treatment resistance, and the acute phase will continue until the patient responds or remits. The aim of the continuation phase is to sustain remission and prevent relapse. During the maintenance phase, the goal is long-term prevention of recurrence in patients who have recovered from an episode of depression.[77]

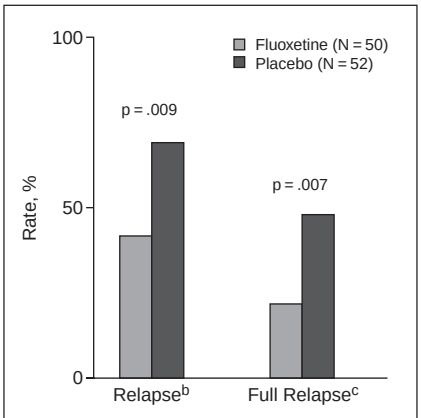
### Treatment-Resistant Depression

Data regarding treatment of pediatric patients who have not responded or achieved remission during the acute phase are scarce. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[78] used 2 major strategies to treat adult patients who did not respond to first-line treatment—switch to another medication or add another medication or CBT. These strategies led to a remission rate of 31% in stage 2 of the study, 14% in stage 3, and 13% for stage 4.[78] Limited data support these approaches in adolescents. One recent study[79] assessed the efficacy of alternative treatments in adolescents who did not respond to 2-month acute treatment with an SSRI. Patients were switched to a different SSRI (paroxetine, citalopram, or fluoxetine) or to venlafaxine, with or without CBT, for 12 weeks. The study found that the addition of CBT (plus the switch to another SSRI or venlafaxine) resulted in higher response rates than switching medications alone.

### Continuation Treatment

The American Psychiatric Association (APA) treatment guidelines[80] for

**Figure 4. Relapse Rates for Children and Adolescents During Continuation Treatment With Fluoxetine or Placebo[a]**




[a]Data from Emslie et al.[83]
[b]Relapse was defined as either a one-time score of ≥ 40 on the Children's Depression Rating Scale–Revised (CDRS–R) with worsening of depressive symptoms for at least 2 weeks, or a clinician determination that full relapse would be likely without altering treatment, even if CDRS–R score was < 40. The survival model was adjusted for gender, age, race, duration of episode, number of episodes, duration of illness, age at illness onset, and baseline continuation phase scores for the CDRS–R, Clinical Global Impression-Severity (CGI-S) scale, Children's Global Assessment Scale, and Family Global Assessment Scale.
[c]Full relapse was defined as a CDRS–R score of ≥ 40. The survival model was adjusted for gender, age, race, duration of episode, number of episodes, duration of illness, age at illness onset, and baseline continuation phase scores for the CDRS–R, CGI-S scale, Children's Global Assessment Scale, and Family Global Assessment Scale.

adult patients recommend, after a patient achieves complete remission in the acute phase, continuation treatment with the same medication and dosage for 4 to 9 months as well as clinical visits every 1 to 3 months. Pediatric guidelines[52,81,82] make similar recommendations to those of the APA.[80] These pediatric guidelines recommend continuing treatment for up to 1 year and monitoring the patient monthly for 6 months after full remission.[35,82]

A relapse prevention study[83] measured the efficacy of fluoxetine during continuation treatment in children and adolescents (7–18 years). In this study, participants were openly treated with fluoxetine for 12 weeks; those who adequately responded during the acute phase were randomly assigned to receive either fluoxetine or placebo for an additional 6 months. Patients had biweekly visits until week 16 and then monthly visits for the rest of the study. During the 6-month continuation phase, relapse rates were statistically significantly higher for placebo-treated patients than for fluoxetine-treated patients (Figure 4). As would be expected, explained Dr. Emslie, the time to relapse was significantly shorter for patients in the placebo group than for patients in the fluoxetine group, and residual symptoms were associated with relapse; therefore, 12 weeks of treatment with only 1 or 2 weeks of being well does not sufficiently prevent relapse.

Before beginning continuation treatment, asymptomatic remission is necessary. Studies[84–86] have shown that patients who have residual symptoms at the end of acute treatment have an increased risk of relapse. Partial remission has been related to poor outcomes in both medication[85,87,88] and CBT trials.[89,90]

Dr. Emslie suggested that sequential treatment may provide the best results. The clinician could treat patients with pharmacotherapy during the acute phase and add CBT during the continuation phase to prevent relapse.

## Maintenance Treatment

After a youth has completely recovered from symptoms and remained stable during continuation therapy of 6 to 12 months, one question remains—should treatment be continued to prevent a new episode of depression? Some guidelines[35,52,82] recommend that maintenance treatment decisions for youths be similar to those for adults. Dr. Emslie stated that, in adults, if the patient has had 3 or more depressive episodes or 2 episodes with other risk factors for recurrence, treatment should probably be continued for life. Maintenance treatment of at least 1 more year may be needed in youths who required longer to remit than other patients or who have had psychosis, comorbidity, suicidality, family disruption or psychopathology, and lack of community support.[35]

Cheung et al.[91] recently published the only data on maintenance treatment in adolescents. In the small study, participants who both responded to treatment with sertraline during the 12-week acute phase and did not relapse during the 24-week continuation phase were randomly assigned to treatment with either sertraline or placebo for an additional 52 weeks. The study found that more sertraline-treated patients remained well compared with placebo-treated patients.

## Conclusion

Dr. Emslie concluded that depression in children and adolescents is a serious and often chronic condition. Although residual symptoms predict relapse, inadequate attention has been given to achieving remission during acute treatment. The goals of treatment for pediatric depression are to reduce the burden of the illness, shorten episodes, and reduce the risk of relapse. Novel sequential treatment strategies may help to prevent relapse and should be studied further.

***Drug names:*** citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

***Disclosure of off-label usage:*** The chair has determined that, to the best of her knowledge, citalopram, escitalopram, mirtazapine, paroxetine, sertraline, venlafaxine, and nefazodone are not approved by the U.S. Food and Drug Administration for the treatment of major depression in children and adolescents.

## REFERENCES

1. National Alliance on Mental Illness. Depression in children and adolescents. 2003. Available at: www.nami.org/Template.cfm?Section=by_illness&template=/ContentManagement/ContentDisplay.cfm&ContentID=17623. Accessed Oct 9, 2008
2. Stein REK, Zitner LE, Jensen PS. Interventions for adolescent depression in primary care. Pediatrics 2006;118:669–682
3. Schulterbrandt JG, Raskin A. Depression in Childhood: Diagnosis, Treatment and Conceptual Models. New York, NY: Raven Press; 1977
4. Lewinsohn PM, Roberts RE, Seeley JR, et al. Adolescent psychopathology 2:

psychosocial risk factors for depression. J Abnorm Psychol 1994;103:302–315
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
6. Klerman GL, Lavori PW, Rice J, et al. Birth-cohort trends in rates of major depressive disorder among relatives of patients with affective disorder. Arch Gen Psychiatry 1985;42:689–693
7. Son SE, Kirchner JT. Depression in children and adolescents. Am Fam Physician 2000;62:2297–2308
8. Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. Psychol Med 1998;28:51–61
9. Weller EB, Weller RA, Danielyan AK. Mood disorders in prepubertal children. In: Wiener JM, Dulcan MK, eds. Textbook of Child and Adolescent Psychiatry. Washington, DC: American Psychiatric Publishing; 2004:411–435
10. National Institute of Mental Health. Women and Depression. 2007. Available at: www.psychcentral.com/lib/2007/women-and-depression/. Accessed Sep 7, 2008
11. Frank E, Young E. Pubertal changes and adolescent challenges. In: Frank E, ed. Gender and Its Effect on Psychopathology. Washington, DC: American Psychiatric Press; 2000:85–102
12. Hankin BL, Abramson LY. Development of gender differences in depression: an elaborated cognitive vulnerability-transactional stress theory. Psychol Bull 2001;127:773–796
13. Sands T, Howard-Hamilton M. Understanding depression among gifted adolescent females: feminist theory strategies. Roeper Review 1995;17:192–196
14. Hankin BL, Abramson LY. Development of gender differences in depression: description and possible explanations. Ann Med 1999;31:372–379
15. Waldinger RJ. Mood disorders. In: Waldinger RJ, ed. Psychiatry for Medical Students. 3rd ed. Washington, DC: American Psychiatric Press; 1997:101–141
16. Weller EB. Mood disorders in children and adolescents. Presented at the 153rd annual meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill
17. Welner Z, Reich W, Herjanic B, et al. Reliability, validity, and parent-child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). J Am Acad Child Adolesc Psychiatry 1987;26:649–653
18. Shaffer D, Fisher P, Dulcan MK, et al. The NIMH Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3): description, acceptability, prevalence rates, and performance in the MECA Study: methods for the Epidemiology of Child and Adolescent Mental Disorders Study. J Am Acad Child Adolesc Psychiatry 1996;35:865–877
19. Weller EB, Weller RA, Fristad MA, et al. Children's Interview for Psychiatric Syndromes. Washington, DC: American Psychiatric Press; 1999
20. Puig-Antich J, Chambers W. The Schedule for Affective Disorders and Schizophrenia for School-Age Children. New York: New York State Psychiatric Association; 1978
21. Luby JL, Belden A, Sullivan J, et al. Preschoolers' contribution to their diagnosis of depression and anxiety: uses and limitations of young child self-report of symptoms. Child Psychiatry and Hum Dev 2007;38:321–338
22. Kovacs M. Children's Depression Inventory Manual. North Tonawanda, NY: Multi-Health Systems; 1992
23. Kovacs M. The Children's Depression Inventory (CDI). Psychopharmacol Bull 1985;21:995–998
24. Beck JS, Beck AT, Jolly J. Manual for the Beck Youth Inventories of Emotional and Social Adjustment. San Antonio, TX: The Psychological Corporation; 2001
25. Reynolds WM. Adolescent Depression Scale: Professional Manual. Odessa, FL: Psychological Assessments Resources; 1987
26. Poznanski EO, Mokros HB. Children's Depression Rating Scale, Revised (CDRS-R) Manual. Los Angeles, CA: Western Psychological Services; 1996
27. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978;133:429–435
28. Steingard RJ, Renshaw PF, Yurgelun-Todd D, et al. Structural abnormalities in brain magnetic resonance images of depressed children. J Am Acad Child Adolesc Psychiatry 1996;35:307–311
29. Steingard RJ, Renshaw PF, Yurgelun-Todd DA. Proton MRS and structural MRI of the orbitofrontal cortex of depressed adolescents. In: The 37th Annual Meeting of the American College of Neuropsychopharmacology; 1998; Las Croabas, Puerto Rico
30. Dahlstrom M, Ahonen A, Ebeling H, et al. Elevated hypothalamic/midbrain serotonin (monoamine) transporter availability in depressive drug-naive children and adolescents. Mol Psychiatry 2000;5:514–522
31. Ward S, Wisner KL. Collaborative management of women with bipolar disorder during pregnancy and postpartum: pharmacologic considerations. J Midwifery Womens Health 2007;52:3–13
32. Way CM. Safety of newer antidepressants in pregnancy. Pharmacotherapy 2007;27:546–552
33. Bar-Oz B, Einarson T, Einarson A, et al. Paroxetine and congenital malformations: meta-analysis and consideration of potential confounding factors. Clin Ther 2007;29:918–926
34. US Food and Drug Administration. Overview of Pregnancy and Lactation Subsection Content and Sample Labels. 2008. Available at: www.fda.gov/cder/regulatory/pregnancy_labeling/summary.htm. Accessed Sep 3, 2008
35. Birmaher B, Brent D, AACAP Work Group on Quality Issues, et al. Practice parameters for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 2007;46:1503–1526
36. Centers for Disease Control and Prevention (CDC). Suicide trends among youths and young adults aged 10–24 years, United States, 1990–2004. 2007. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/mm5635a2.htm. Accessed Sep 1, 2008
37. National Adolescent Health Information Center. 2006 Fact sheet on suicide: adolescents and young adults. Available at: www.nahic.ucsf.edu/downloads/Suicide.pdf. Accessed Sep 1, 2008
38. National Center for Injury Prevention and Control. Leading causes of death and fatal injuries: mortality reports (2006). Available at: www.cdc.gov/ncipc/wisqars/. Accessed Sep 1, 2008
39. Brent DA, Baugher M, Bridge J, et al. Age and sex-related risk factors for adolescent suicide. J Am Acad Child and Adolec Psychiatry 1999;38:1497–1505
40. Bridge JA, Goldstein TR, Brent DA. Adolescent suicide and suicidal behavior. J Child Psychol and Psychiatry 2006;37:372–394
41. Whittington CJ, Kendall T, Fonagy P, et al. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 2004;363:1341–1345
42. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332–339
43. Libby AM, Brent DA, Morrato EH, et al. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry 2007;164:884–891
44. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 2007;297:1683–1696
45. March JS, Silva S, Petrycki S, et al. The Treatment of Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. Arch Gen Psychiatry 2007;64:1132–1143
46. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54:1031–1037
47. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002;41:1205–1215
48. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 2004;292:807–820
49. Wagner KD, Robb AS, Findling RL, et al. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. Am J Psychiatry 2004;161:1079–1083
50. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. JAMA 2003;290:1033–1041
51. Emslie GJ, Bose A, Ventura D, et al. Escitalopram in the treatment of adolescent depression. Presented at the 161st annual meeting of the American Psychiatric Association; May 3–8, 2008; Washington, DC
52. Hughes CW, Emslie GJ, Crismon ML, et al.

Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. J Am Acad Child Adolesc Psychiatry 2007; 46:667–686
53. Berard R, Fong R, Carpenter DJ, et al. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. J Child Adolesc Psychopharmacol 2006;16:59–75
54. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2001;40:762–772
55. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry 2006;45:709–719
56. Wagner KD, Jonas J, Findling RL, et al. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. J Am Acad Child Adolesc Psychiatry 2006;45:280–288
57. Organon Pharmaceuticals USA, Inc. A multi-center, randomized, double-blind, placebo-controlled, efficacy and safety study of Remeron in outpatient children and adolescents with major depressive disorder. 2001. Available at: www.clinicalstudyresults.org/documents/company-study_51_0.pdf. Accessed Sep 5, 2008
58. Mosholder, AD, reviewer. Review and evaluation of clinical data. 2002. Available at: www.fda.gov/cder/foi/esum/2004/20152s032_Serzone_clinical_BPCA_FIN.pdf. Accessed Sep 5, 2008
59. von Knorring AL, Olsson GI, Thomsen PH, et al. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. J Clin Psychopharmacol 2006;26:311–315
60. Emslie GJ, Findling RL, Yeung PP, et al. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. J Am Acad Child Adolesc Psychiatry 2007;46:479–488
61. Emslie GJ, Ryan ND, Wagner KD. Major depressive disorder in children and adolescents: clinical trial design and antidepressant efficacy. J Clin Psychiatry 2005; 66(suppl 7):14–20
62. Weersing VR, Brent DA. Cognitive behavioral therapy for depression in youth. Child Adolesc Psychiatr Clin N Am 2006;15:939–957
63. Klomek AB, Mufson L. Interpersonal psychotherapy for depressed adolescents. Child Adolesc Psychiatr Clin N Am 2006; 15:959–975
64. Brent DA, Holder D, Kolko D, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. Arch Gen Psychiatry 1997;54:877–885
65. Rohde P, Clarke GN, Mace DE, et al. An efficacy/effectiveness study of cognitive-behavioral treatment for adolescents with comorbid major depression and conduct disorder. J Am Acad Child Adolesc Psychiatry 2004;43:660–668
66. Mufson L, Weissman MM, Moreau D, et al. Efficacy of interpersonal psychotherapy for depressed adolescents. Arch Gen Psychiatry 1999;56:573–579
67. Mufson L, Dorta KP, Wickramaratne P, et al. A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. Arch Gen Psychiatry 2004;61: 577–584
68. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. Psychol Bull 2006;132:132–149
69. Watanabe N, Hunot V, Omori IM, et al. Psychotherapy for depression among children and adolescents: a systematic review. Acta Psychiatr Scand 2007;116:84–95
70. Kennard B, Silva S, Vitiello B, et al. Remission and residual symptoms after short-term treatment in the Treatment of Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry 2006;45:1404–1411
71. Vitiello B, Rohde P, Silva S, et al. Functioning and quality of life in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Adolesc Psychiatry 2006;45:1419–1426
72. Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents With Depression Study (TADS). J Am Acad Child Adolesc Psychiatry 2006;45:1427–1439
73. Goodyer I, Dubicka B, Wilkinson P, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behavior therapy in adolescents with major depression: randomised controlled trial. BMJ 2007; 335:142–146
74. Melvin GA, Tonge BJ, King NJ, et al. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. J Am Acad Child Adolesc Psychiatry 2006;45: 1151–1161
75. Byford S, Barrett B, Roberts C, et al. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioral therapy in adolescents with major depression. Br J Psychiatry 2007;191:521–527
76. Kennard BD, Emslie GJ, Mayes TL, et al. Relapse and recurrence in pediatric depression. Child Adolesc Psychiatr Clin N Am 2006;15:1057–1079
77. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48: 851–855
78. Rush AJ, Trivedi JH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905–1917
79. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA 2008;299:901–913
80. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
81. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 2007;46:1503–1526
82. Cheung AH, Zuckerbrot A, Jensen PS, et al. Guidelines for adolescent depression in primary care (GLAD-PC), 2: treatment and ongoing management. Pediatrics 2006;120:e1313–e1326
83. Emslie GJ, Kennard BD, Mayes TL, et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. Am J Psychiatry 2008; 165:459–467
84. Cornwall P, Scott J. Partial remission in depressive disorders. Acta Psychiatr Scand 1997;95:265–271
85. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;50:97–108
86. Keller MB. Remission versus response: the new gold standard of antidepressant care. J Clin Psychiatry 2004;65(suppl 4):53–59
87. Faravelli C, Ambonetti A, Pallanti S, et al. Depressive relapses and incomplete recovery from index episode. Am J Psychiatry 1986;143:888–891
88. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25:1171–1180
89. Simons A, Murphy G, Levine J, et al. Cognitive therapy and pharmacotherapy for depression: sustained improvement over one year. Arch Gen Psychiatry 1986;43:43–48
90. Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behavioral therapy of depression: potential implications for longer courses of treatment. Am J Psychiatry 1992;149:1046–1052
91. Cheung A, Kusumaker V, Kutcher S, et al. Maintenance study for adolescent depression. J Child Adolesc Psychopharmacol 2008;18:389–394

For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 1839–1841.