ADOLESCENT DEPRESSION: An Update and Guide to Clinical Decision Making

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ABSTRACT

Depression in adolescence and adulthood is common, afflicting up to 20 percent of these populations. It represents a significant public health concern and is associated with considerable suffering and functional impairment. Adolescent-onset depression tends to be a particularly malignant and recalcitrant condition, increasing the likelihood of recurrence and chronicity in adulthood. Clinical presentations for various medical and psychiatric conditions, as well as reactions to psychosocial stressors, can mimic or confound the picture of depression in adolescents. Therefore, careful assessment and differential diagnosis is essential. Effective treatments, both pharmacological and psychosocial in nature, exist, and so early detection and intervention is paramount. This article presents an overview of optimal prevention, assessment, and clinical decision-making strategies for managing depression in adolescents.

A CASE VIGNETTE

(This is a composite case and is not based on an actual patient in treatment.) Julia was a 16-year-old girl who reported difficulty sleeping, an irritable mood, low energy, and declining grades for the past several

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months. She was accompanied by her mother who was very worried. The mother reported that Julia quit the tennis team, which she used to enjoy, and lost weight. Julia initially said these problems were "not that bad" and that her mother needed to "stop hassling me."

INTRODUCTION

Depression is one of the most costly and debilitating medical conditions afflicting our society.[1] It is a leading cause of absenteeism and compromised productivity in adults, costing the US economy billions of dollars per year.[2] It also worsens the course and increases the cost of numerous medical illnesses. It contributes to premature death by suicide.[3] The impact of depression reverberates well beyond its victims, affecting family and friends. Recognizing and treating major depression and its variants in the early stages is important in reducing future negative impact.

Depression in adolescence significantly impairs functioning and may derail normal psychosocial development. Moreover, it often recurs or persists into adulthood. Rates of depression rise considerably during adolescence with as many as one in five teenagers developing major depression at some point. In adolescence, depression can be mistaken for adolescent angst or for hormone-related moodiness although it is a disorder associated with serious consequences. Youth with depression are likely to suffer broad functional impairment across social, academic, family, and occupational domains.[4] Adolescents with depression are at higher risk for substance abuse and other psychiatric comorbidities.[4] In addition, depression disorders with a pediatric onset tend to be more chronic and debilitating than depression beginning in adulthood.[5] Fortunately, we now have an array of evidence-based pharmacological and psychotherapeutic treatments for depression.

PREVENTION

The literature on prevention of depression in youth has grown substantially in the past decade but has been plagued by methodological limitations; therefore, identification of effective preventive strategies remains in its early stages. Programs that have been universally applied to community samples have been largely, but not entirely, ineffectual. In general, programs with interventions delivered by the research team, psychologists, or extensively trained group leaders, have been associated with the greatest success.[6] Skill sets taught in some of the more effective interventions have included cognitive restructuring, problem solving, stress management, and accessing social support. Programs that have offered less training or for which interventions were delivered by nonmental health professionals (e.g., teachers) have tended to produce less favorable outcomes.

The most successful strategy identified thus far involves both targeting at-risk cohorts and utilizing expert clinicians to deliver treatments. Research has repeatedly documented increased prevalence of major depression in the offspring of depressed parents.[7] Programs that specifically target children of depressed parents have been more effective.[8,9] An alternative strategy for identifying risk involves screening adolescents for depression and applying interventions specifically to teens with subsyndromal depression.[10] This strategy has been associated with reduced risk for depression onset, as well as a significant delay in onset of depression. Selecting a well-established risk factor (parental depression, subsyndromal depression), examining the mechanisms by which risk is imposed, and attempting to augment protective factors is a sound model for conducting prevention research.

EPIDEMIOLOGY

Depressive symptoms are common in pediatric clinical settings, with 5 to 10 percent of children and adolescents presenting with subsyndromal symptoms of major depressive disorder (MDD).[11] MDD is estimated to affect two percent of children aged 6 to 12 years and 4 to 8 percent of adolescents aged 13 to 17 years. In children, the ratio of boys to girls is 1:1, but in teens, the ratio changes to 1:2. Dysthymic disorder (DD), which constitutes a more chronic, milder form of depression, has been reported to afflict 0.6 to 1.7 percent of children and 1.6 to 8 percent of adolescents. The risk of depression increases significantly after puberty (particularly in girls), and by age 18, the cumulative incidence is 20 percent.[12]

RISK FACTORS

A family history of depression has consistently been found as a risk factor for the disorder. High-risk, adoption, and twin studies have demonstrated that MDD is caused by the interaction of genetic and environmental risk factors, with an interplay between life stressors and a serotonic transporter polymorphism reported as one causal pathway.[13–16] Subsyndromal symptoms of depression, low self esteem, and anxiety have all been found to increase the probability of developing depression. Academic struggles and family turmoil are also prospective predictors of depression for teenagers.[17] Consistent with cognitive models of depression, a negative attributional style in combination with negative life events can lead to the development of depression.[18]

SCREENING AND ASSESSMENT

Primary care providers should screen all youth for depression by asking about key symptoms, including sad or irritable mood and anhedonia or the inability to experience pleasure and have fun. In youngsters, readily observable changes associated with onset of depression might include deteriorating academic performance, weight or appetite loss or gain,

social withdrawal, changes in sleep, increased defiance (related to irritability), and discontinuation of previously preferred activities. Teenagers with increased negative moods should be further assessed for changes in thinking to a more negative view of themselves, the world, and the future. Asking about suicidal ideation and screening for safety are also important parts of the interview.

The clinical presentation of depression in youth resembles that in adults with some differences stemming from developmental considerations. For instance, children are more likely than adults to exhibit mood lability or irritability and display indirect or behavioral manifestations of disturbed mood, such as temper outbursts, somatic complaints, social withdrawal, or diminished frustration tolerance. They are less likely than adults to explicitly complain of feeling depressed and unlikely to exhibit melancholic symptoms, including depressed mood worse in the morning, early morning awakening, marked psychomotor retardation, significant weight loss, and excessive guilt.

Depression in youth may be accompanied by hallucinations or delusions, although rarely. Psychotic depression in children has been associated with a family history of bipolar and depression with psychotic features, more severe depression, greater long-term risk, resistance to antidepressants, and increased risk of future onset of bipolar disorder.[19,20] Youth with seasonal affective disorder (SAD) mainly have symptoms of depression during seasons with less daylight. SAD should be differentiated from depression triggered by school stress because both usually coincide with the school calendar.

A diagnosis of a depressive disorder would be considered if the youth demonstrated markedly impaired functioning in social, academic, or family domains. Functionality can be readily and objectively assessed using the Children's Global Assessment Scale or Global Assessment of Functioning. Complaints of significant emotional distress in the child would also merit further investigation for depressive symptoms. Screening can be facilitated by using depressive symptom checklists derived from the *Diagnostic and Statistical manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*)[21] or *the International Classification of Diseases, Tenth Revision* (*ICD-10*),[22] clinician-based instruments, or youth or parent self reports. Examples of widely used and well-validated screening checklists include the Child Depression Inventory, as well as the Reynold's Adolescent Depression Scale.[12]

Youth do not always readily report on emotional or behavioral manifestations of psychiatric disorders. They might deny the existence of these symptoms or behaviors or simply have difficulty articulating their thoughts and feelings. The use of open-ended or indirect questions is recommended in pediatric interviews, as the information collected is likely to be more comprehensive and reliable. Direct or closed-ended questions tend to elicit more limited and potentially biased responses from children and teens, due to their leading nature and the tendency of youth to be suggestible. Collateral information from parents, alternative caregivers, and teachers is often essential for confirming or ruling out depression or other psychiatric or behavioral disorders. The onset and course of a mood disorder may be determined through the use of a mood diary or timeline, using significant life events as anchors. A mood timeline can enable the provider, child, and parents to identify environmental triggers, as well as comorbid conditions.

DIAGNOSTIC CRITERIA

Depression is manifested as a spectrum disorder, ranging from subsyndromal to syndromal. Criteria for the full syndrome of MDD are met when a child or adolescent presents with at least two weeks of a persistent change in mood, depressed or irritable, plus at least five of the nine symptoms listed in Table 1. The symptoms must be impairing, represent a change from baseline functioning, and not be attributable to another psychiatric or medical etiology, bereavement, or substance abuse. MDD can be manifested with atypical symptoms, such as increased reactivity to rejection, lethargy (leaden paralysis), increased appetite, craving for carbohydrates, and hypersomnia.

Dysthymic disorder consists of a persistent, long-term change in mood that generally is less intense but more chronic than in MDD. Due to its more subtle and chronic nature, DD is often overlooked or misdiagnosed. Although the symptoms of dysthymia are not as severe as in MDD, they nonetheless typically cause as much or more psychosocial impairment. Criteria for DD are met when a child or adolescent presents with at least one year of a depressed or irritable mood most of the time, and at least two other symptoms from the group listed in Table 1.

DIFFERENTIAL DIAGNOSIS

There are a myriad of psychiatric conditions with significant symptomatic overlap with depression, such as anxiety and disruptive, psychotic, and substance use disorders, to name a few. Bereavement and depressive reactions to environmental stressors can likewise present with predominately depressive symptomatology. Youths with SAD, by definition, develop depressive symptoms coincident with seasons having diminished daylight. SAD can be confused with depression precipitated by school stress as both conditions coincide with the school calendar.

Various medical conditions, including hypothyroidism, anemia, autoimmune diseases, and chronic

TABLE 1. Criteria for major depressive episode and dysthymic disorder*

MAJOR DEPRESSIVE EPISODE—Five (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition or mood-incongruent delusions or hallucinations.
Depressed or irritable mood most of the time
Diminished interest or pleasure in most activities
Weight (or appetite) loss or gain
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation observed by others
Fatigue/energy loss nearly every day
Feelings of worthlessness or inappropriate guilt
Decreased concentration or indecisiveness
Recurrent thoughts of death or suicidal ideation
DYSTHYMIC DISORDER—Depressed or irritable mood for most of the time for at least one year. Presence, while depressed, of at least two of the following:
Poor appetite or overeating
Insomnia or hypersomnia
Fatigue or low energy
Low self esteem
Poor concentration or difficulty making decisions
Feelings of hopelessness

*Based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*[21]

fatigue syndrome may mimic or occur coincidentally with depression. Symptoms shared between these conditions and depression might include fatigue, low energy, sleep and appetite disturbances, and impaired concentration. Demoralization and low self esteem commonly manifest as part of the aforementioned disorders and so, too, are expected symptoms of depression. Therefore, physical examination and screening for such conditions may be warranted.

Practitioners must be mindful of the extensive list of medications that can produce depressive symptoms. For instance, stimulants, corticosteroids, and contraceptives are often associated with worsening mood lability or irritability. They likewise can disturb sleep and appetite as well as induce weight changes.

Children presenting for treatment are often experiencing their first episode of depression, making it difficult to ascertain whether or not they are experiencing unipolar depression or the first episode of a bipolar disorder. A strong family history of bipolar disorder, symptoms of psychosis in the child, and a history of pharmacologically induced mania or hypomania increase the likelihood of future onset of a bipolar disorder.[19,20] It is prudent for clinicians to systematically screen for a history of manic or hypomanic symptoms because such a history predicts which youth are more likely to experience medication-induced mania when treated with antidepressants.

It is important to note, however, that not all children who become "activated" or hypomanic while receiving antidepressants have bipolar disorder. A common side effect of serotonergic agents is akathisia or extreme restlessness and agitation. This reaction is likely to occur early in treatment (within a few days) and consists of extreme motoric overactivity without concomitant mood symptoms. Mania or hypomania induced by serotonergic agents might also include a hyperactive motor component, but this generally occurs later in treatment (after 2 or more weeks) and would be accompanied by elevated, euphoric, or irritable mood, grandiosity, decreased need for sleep, and hypersexuality.

CASE VIGNETTE, CONTINUED

When Julia was interviewed separately, the clinician was able to establish a therapeutic alliance with the teenager. Julia described her problems in more detail with the clinician. Julia described thoughts of suicide over the past several weeks, although she did not have any specific plan and she had not attempted to harm herself.

SUICIDALITY

Suicide remains the third leading cause of death in US adolescents, claiming almost 2,000 lives each year among youth aged 12 to 19 years.[3] Almost 1 in 5 (17%) of US high school students had suicidal thoughts in a given year, and almost 1 in 10 (8%) have attempted suicide. Current suicidal ideation is a risk factor for suicide, and having made a suicide attempt is the strongest predictor of future suicidal behavior.[23,24] Suicidal ideation is common among depressed youth, with an estimated 60 percent

reporting having had suicidal thoughts and 30 percent reporting a suicide attempt.[12]

Acutely suicidal, psychotic, self-harming, or severely depressed children and adolescents should have an emergency psychiatric consultation. A comprehensive approach is outlined in Table 2. The thorough assessment of teens who are suicidal should involve interviewing the adolescent separately from the family and obtaining collateral information from parents, therapists, teachers, caseworkers, and others, as needed. The teen will likely respond best to an empathic, nonjudgmental demeanor, and the clinician should ask about current and past self-harming behaviors. Inquiring about suicidal thoughts (frequency, duration, plans, and "triggers"), suicide intent (intensity of the desire to die), and past suicide attempts (number of attempts, methods, consequences) is essential. Targeted questions about suicidality have not been associated with precipitating increased suicidal thinking in youth, and, in fact, literature on this topic has suggested such questioning tends to bring relief to troubled teens. Questions should be asked about acute stressors (e.g., break up, loss or rejection, conflict with parents), presence of psychotic symptoms or homicidal thoughts, and the extent of any substance abuse. Parents or guardians should be involved in the evaluation, safety planning, and treatment process.

Psychiatric hospitalization is appropriate for youth with active suicidal thoughts or recent suicidal or self-injurious behaviors. It might also be indicated for patients presenting with acute psychiatric disorders, significant substance abuse problems, serious medical issues, poor social supports, or an inability to be safely managed on an outpatient basis. A comprehensive approach is outlined in Table 2.

CASE VIGNETTE, CONTINUED

As the interview progressed, Julia seemed to open up more, describing her increased use of alcohol and marijuana since she and her boyfriend broke up three months previously. Since the break up, Julia felt she was not able to "bounce back" the way that she had before.

COMORBIDITY

Both MDD and DD are commonly associated with other psychiatric and medical conditions. In addition, they often occur concurrently, a condition termed *double depression*. Epidemiological studies have estimated that 40 to 90 percent of youth presenting with depression also met criteria for an additional psychiatric disorder, with up to 50 percent manifesting two or more comorbid psychiatric diagnoses.[25,26] The most frequent comorbid diagnoses are anxiety disorders, followed by disruptive behavior disorders, including attention deficit hyperactivity disorder, and, in adolescents, substance use disorders. MDD and DD usually onset later than anxiety, but prior to other psychiatric conditions, including conduct and substance abuse disorders.

SITUATIONAL PROBLEMS

Depression is theorized as stemming from an interaction between a depressive diathesis and psychosocial stressors.[27,28] Therefore, careful assessment for current and past stressors is indicated, including interpersonal or family conflict; verbal, physical, and sexual abuse; neglect, or poverty. It is also important to assess for symptoms consistent with posttraumatic stress disorder, which can develop in response to traumatic events. Depression often occurs against a backdrop of interpersonal and family conflict. Depression tends to increase irritability, leading to increased interpersonal tension and estrangement of others. Patients with depression consequently often perceive diminishing social support and increasing loneliness, limiting opportunities for pleasure and further exacerbating depression. Involvement in deviant peer groups may lead to antisocial behavior, generating more stressful life events and increasing the likelihood of depression.[29,30]

The family should be evaluated for psychiatric illness to facilitate establishing a definitive diagnosis and treatment plan for the child, because parental psychopathology often predicts adherence with treatment, course of illness, and outcome. It is essential to assess for marital and family discord, impaired attachment, inadequate parent support, and controlling parent-child relationships, because these factors can increase risk for substance abuse and conduct disorder.

CLINICAL COURSE

Clinically referred youth with major depression will have a median episode duration of eight months, whereas community samples experience a median duration of 1 to 2 months.[31] Nearly all children and adolescents will recover from their first depressive episode, but long-term clinical and epidemiological studies have demonstrated probability rates of recurrence ranging from 20 to 60 percent by 1 to 2 years after remission and rising to 70 percent after five years. A significant proportion of youth with MDD will continue to suffer from MDD during adulthood.[19,32] Between 20 and 40 percent of pediatric patients presenting with depression will develop bipolar disorder at some point.[19,20] Those especially at risk include patients presenting with concomitant psychotic features and family histories of bipolar and those with histories of pharmacologically induced mania or hypomania.

Childhood depression appears to be more heterogeneous than its adult counterpart. Children with significant genetic loading for mood disorders are at particular risk for recurrences whereas others are likely to develop bipolar disorder. Some youth presenting with symptoms and behaviors that initially resemble depression develop behavior problems and substance abuse rather than depression.

Poor outcomes are associated with greater severity, chronicity or

TABLE 2. The suicidal/self-harming adolescent
PSYCHIATRIC INTERVIEW SHOULD ADDRESS THE FOLLOWING:
Acute stressors (e.g., romantic break up, school failure)
Recurrent thoughts of past stress, abuse, or trauma
Substance abuse, psychosis, and other diagnoses, in addition to depression
Self-injurious behavior, associated thoughts, reasons for self harm (coping strategy vs. wish to die)
Frequency and duration and intensity of suicidal thoughts
Suicidal intent, plans, and access to lethal implements or drugs
History of suicide attempts
Family history of suicide and friends who have died
Availability of interpersonal resources and support
ASSESSMENT APPROACH
Use a calm, nonjudgmental approach
Be firm about need to establish safety
Spend at least part of the interview with the teen alone
Obtain collateral information from parents/family, therapist, caseworkers, and others
Conduct physical exam and consider routine labs and urine toxicology screen
SUICIDE RISK FACTORS:
Diagnoses: major depressive disorder, substance abuse, conduct disorder, and psychotic disorders
Demographics: older teens attempt and complete suicide more often; females have more attempts, but males complete suicide more often and use more lethal means
Recent life events: academic or legal problems, recent loss of family, friends
Sexuality issues: break up of romance, gender identity conflicts
Past life events: youth history of attempts, family suicide, history of physical or sexual abuse
Interpersonal: poor family communication, lack of peer support
Environmental: access to lethal means, exposure to suicide in the community or media
INPATIENT TREATMENT IS RECOMMENDED WITH THE FOLLOWING:
Persistent and/or intense thoughts of suicide
Specific suicidal plans or previous suicide attempts
History of impulsive and dangerous behaviors
Severe depression, psychosis (especially with command hallucinations), and/or substance abuse
Inability to specify plans to support safety
Lack of adequate support from family and/or friends
OUTPATIENT TREATMENT MAY BE CONSIDERED WITH THE FOLLOWING:
Transient or fleeting thoughts of suicide, but none currently
Ability of youth to articulate reasons to live
Secure environment that limits access to lethal means, especially firearms
Parental awareness of contributing risks including substance use
Youth, family, and clinician agreement on plan to monitor safety
Plan for coping with dangerous or overwhelming thoughts or feelings
Psychotherapy is scheduled to begin or continue
Youth and family are able to articulate plans for emergencies

recurrence, comorbid conditions, hopelessness, residual subsyndromal symptoms, pessimism, family discord, low socioeconomic status, and chronic environmental stressors (abuse, family conflict).[11,25] Children with DD are likely to experience a prolonged course of illness, with a mean episode length of 3 to 4 years for clinical and community samples.[26] In addition, this disorder is further associated with increased risk of subsequent development of MDD and substance abuse.

LONG-TERM PROGNOSIS

Untreated depression in children is likely to derail their emotional, cognitive, and social development, in addition to impairing family relationships. The most devastating consequences of MDD are suicide attempts and completions. Approximately 60 percent of depressed youth report having thought about suicide and 30 percent actually attempt suicide.[3] The risk of suicidality is increased by a history of suicide attempts, comorbid psychiatric disorders (e.g., disruptive disorders, substance abuse), impulsivity, aggression, access to lethal methods (e.g., firearms), exposure to negative events (e.g., physical or sexual abuse, violence), and a family history of suicidal behavior.[23,24,33,34]

Pediatric patients with depression are additionally at particularly high risk for substance abuse (including nicotine dependence), legal problems, adverse events, physical illness, early pregnancy, and poor work, academic, and psychosocial outcomes.[25,19,32,35]

Psychosocial functioning is likely to gradually improve after an acute depressive episode except, of course, in the face of relapse. However, psychosocial difficulties typically persist even after remission of a depressive episode, highlighting the need for ongoing monitoring and treatment that targets psychosocial and environmental issues.

CASE VIGNETTE, CONTINUED

After a physical exam and laboratory studies showed no significant abnormalities, Julia was diagnosed with MDD and there was a discussion of treatment options. When antidepressant medication was mentioned, Julia and her mother expressed concerns that antidepressants can cause suicide. They also wanted to know whether medication or psychotherapy was better as a treatment approach.

PHARMACOLOGICAL TREATMENT

The use of pharmacologic agents to treat pediatric depression has been shrouded in controversy in recent years. The controversy stems from a relative paucity of controlled data documenting efficacy for antidepressants in youth and some data demonstrating a small but significant signal of increased suicidality associated with the initiation of some antidepressants. Numerous studies have examined the utility of tricyclic antidepressants (TCAs) to treat pediatric depression, all of which have been negative.[4] This data, together with a relatively high potential for lethality in overdose, have led to the consensus that TCAs are contraindicated for treating youth with depression. Until recently, the only agent to receive US Food and Drug Administration (FDA) approval for the indication of major depression in 8- to 17-year-olds was fluoxetine. Recently, escitalopram was approved by the FDA for the treatment of depression in adolescents.[36,37] Other antidepressants are frequently still used for pediatric depression, but their use is considered off label.

Efficacy data. The results of randomized, controlled trials comparing selective serotonin reuptake inhibitor (SSRI)-treatment of MDD in adolescents are shown in Table 3. The efficacy of fluoxetine for pediatric MDD has been demonstrated in several controlled trials.[39–41] The results of three paroxetine trials[42,43] and two sertraline trials[44] suggest equivocal or weakly positive efficacy. Likewise, efficacy of citalopram was supported by one published trial, but not by an unpublished one.[38] For venlafaxine and mirtazapine, two unpublished trials for each compound did not demonstrate efficacy.[45,38]

A landmark study, the Treatment for Adolescents with Depression Study (TADS), was a National Institute of Mental Health (NIMH)-sponsored, multisite trial comparing fluoxetine, cognitive behavioral therapy (CBT), their combination, and placebo in 439 adolescents with a primary diagnosis of major depression.[47] After 12 weeks of treatment, fluoxetine alone was shown to be effective in treating adolescent depression. However, the combination of fluoxetine and CBT was statistically superior to placebo, CBT, and fluoxetine alone. While fluoxetine may help initiate a faster treatment response, extending the study to 36 weeks showed further support for the use of the combination treatment in adolescents with moderate to severe depression.[47]

Based upon these clinical trials, fluoxetine and escitalopram appear to have efficacy in the treatment of pediatric depression, with the majority of the trials demonstrating positive results. Some support for efficacy also exists for sertraline and citalopram. However, the efficacy signal for these drugs is weaker and inconsistent. It is possible the variability in outcome is similar to what is seen in adult literature, where antidepressants approved by the FDA for the treatment of adult MDD frequently have as many negative as they do positive trials. No evidence of efficacy exists for venlafaxine, paroxetine, or mirtazapine. Whether the discrepancies in treatment efficacy between the SSRIs is better explained by methodological factors or by substantive pharmacological differences continues to be debated.

Relapse prevention. Rates of recurrence of depression in youth have been found to be strikingly high among clinical and community samples, reaching 20 to 60 percent by 1 to 2 years and 70 percent after five years.[19,32] At least one controlled

TABLE 3. Primary outcome results for acute (8–12 week), placebo-controlled, pediatric studies of SSRIs and related serotonergic drugs in major depression

DRUG	PUBLICATION	N	PRIMARY OUTCOME MEASURE	AGE RANGE	RESULT
Paroxetine	Keller et al 2001**	275	HAM-D	12–18	Negative
Paroxetine	Berard et al 2006	275	MADRS	13–18	Negative
Paroxetine	Emslie et al 2007	203	CDRS-R	7–17	Negative
Fluoxetine	Emslie et al 2002	219	CDRS-R	8–18	Positive
Fluoxetine	Emslie et al 1997	96	CDRS-R	8–17	Positive
Fluoxetine	TADS 2004	439	CDRS-R	12–17	Positive
Sertraline	Wagner et al 2003***	160	CDRS-R	6–17	Trend*
Sertraline	Wagner et al 2003***	160	CDRS-R	6–17	Negative
Venlafaxine	Unpublished	161	CDRS-R	7–17	Negative
Venlafaxine	Unpublished	193	CDRS-R	7–17	Negative
Citalopram	Wagner et al 2004	174	CDRS-R	7–17	Positive
Citalopram	Unpublished	244	CDRS-R	13–18	Negative
Nefazodone	Unpublished	195	CDRS-R	12–18	Trend*
Nefazodone	Unpublished	273	CDRS-R	7–17	Negative
Mirtazapine	Unpublished	126	CDRS-R	7–17	Negative
Mirtazapine	Unpublished	124	CDRS-R	7–17	Negative
Escitalopram	Emslie et al 2009	312	CDRS-R	12-17	Positive

Source: Adapted from Laughren TP. Memorandum, January 5, 2004: Background comments for February 2, 2004, Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (AC), Bethesda, Maryland.

*Positive ($p< 0.05$); negative ($p>0.10$); Trend ($0.05<p<0.10$) on primary efficacy outcome.
**Keller et al 2001—positive on most secondary endpoints.
***Wagner et al 2003—positive on pooling of two studies.

KEY: SSRIs=selective serotonin reuptake inhibitors; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale; CDRS-R=Childhood Depression Rating Scale—Revised.

trial demonstrated a significant reduction in the risk of relapse, from 69 to 42 percent, when fluoxetine was continued beyond the acute phase of treatment, through the "continuation" phase, which extended an additional 6 to 9 months.[48] Adult studies have similiarly shown a significant reduction in relapse rates when antidepressants were continued for 6 to 9 months beyond acute treatment. As has also been reported with adults, there is a significant reduction in relapse rates for patients who receive CBT as a continuation treatment.[49]

Relapse in both pediatric and adult populations is much less likely in patients who exhibit a complete response to acute treatment. On the other hand, patients with persistent residual depressive symptoms, even after meeting threshold for response to treatment criteria, are at a significantly higher risk for recurrence.[10] Thus, the goal of treatment has increasingly become total wellness or complete response. Furthermore, even subsyndromal, residual depressive symptoms are associated with meaningful impairment.

Safety data. In September 2004, when the FDA presented results of their meta-analysis of 25 trials plus TADS, safety data were presented along with efficacy data.[38] An independent team of experts utilized an approach developed by researchers at Columbia University to evaluate and recode all adverse events for suicidal and self-injurious behaviors (suicide attempt, preparatory acts, suicidal ideation, and so forth). Following reclassification, 78 of the approximately 4,400 subjects from these datasets (1.7%) were coded as experiencing either suicidal behavior (n=33) or suicidal ideation (n=45). There were no completed suicides, and only venlafaxine and fluoxetine in the TADS study exhibited a statistically significant signal for suicidality (suicide attempts or suicidal ideation). The overall relative risk (RR) for suicidality was

1.66 (95% CI; 1.02, 2.68) for MDD trials and 1.95 (1.28, 2.98) for all medication trials, for all indications.[38] The authors of the analysis concluded, "Although the difference is small, it seems likely that the effect is real, because the findings were statistically significant in aggregate and are consistent across multiple studies of various agents."[38] The overall risk difference for the SSRIs in the MDD trials is approximately two percent. In other words, two patients of 100 treated with an SSRI for major depression would be expected to have an increase in suicidality during short-term treatment, attributable specifically to the drug. The relative risk of suicidality by specific antidepressant is listed in Table 4. Suicidality, when it did occur, was primarily ideation, with only a minority of events involving actual suicide attempts (27 suicide attempts, 6 "preparatory actions," and 45 suicidal ideation events).

In addition to an increase in the risk of suicidality, SSRIs are almost twice as likely as placebo to cause increased agitation and hostility during acute treatment, with the relative risk by specific antidepressant listed in Table 5. It remains unclear whether the increased risk for suicidality associated with these medications is mediated by the agitation and hostility symptoms. Nonetheless, it is important for patients and families to be aware of this potential.

The advisory committee to the FDA concluded that the adverse events reported voluntarily during clinical trials in aggregate indicated an increased risk of treatment-emergent suicidality. Although there was variability in the adverse event data, the committee was unable to conclude that any single antidepressant was without risk. Since the FDA's October 2004 "black box" warning and additional recommendations regarding antidepressant use in children, other regulatory bodies in Europe and Canada have also released warnings.

TABLE 4. Overall relative risks of suicidal behavior or ideation by drugs in MDD trials as defined by the Columbia University Reclassification Project[50]

DRUG	RELATIVE RISK (95% CI) MDD TRIALS	RELATIVE RISK (95% CI) ALL TRIALS
Citalopram	1.37 (0.53, 3.50)	1.37 (0.53, 3.50)
Fluvoxamine	No MDD trials	5.52 (0.27, 112.55)
Paroxetine	2.15 (0.71, 6.52)	2.65 (1.00, 7.02)
Fluoxetine	1.53 (0.74, 3.16)	1.52 (0.75, 3.09)
Sertraline	2.16 (0.48, 9.62)	1.48 (0.42, 5.24)
Venlafaxine	8.84 (1.12, 69.51)	4.97 (1.09, 22.72)
Mirtazapine	1.58 (0.06, 38.37)	1.58 (0.06, 38.37)
Nefazodone	No events	No events
Bupropion	No MDD trials	No events

MDD = major depressive disorder; CI = Confidence Interval.

TADS provided a systematic approach to collecting data on suicidality, beginning at baseline and continuing to all subsequent endpoints, allowing for a longer-term assessment of the role of various treatments on suicide. At baseline, clinically significant suicidal thinking was present in 29 percent of the sample. Suicidality declined significantly in all four treatment groups with fluoxetine plus CBT showing the greatest reduction (p=0.02). There were no completed suicides in the course of the study, but 24 (5.5%) of the 439 TADS patients experienced a suicide-related event. Seven (7) of the 24 suicide-related events were suicide attempts (1.6% of the total sample). Four (4) of the attempts were by patients assigned to fluoxetine and CBT, two to fluoxetine alone, and one to CBT alone. None of the subjects taking placebo attempted suicide.

Harm-related events, which included thoughts or behaviors related to harm of self as well as harm to others, occurred in 11.9 percent of those assigned to fluoxetine alone, 8.4 percent fluoxetine with CBT, 4.5 percent CBT alone, and 5.4 percent placebo. Overall, suicidality decreased with treatment. Improvement was greatest for those receiving combination treatment and least for those receiving fluoxetine alone. It is important to note that, though fluoxetine did not appear to increase suicidal ideation, the harm-related adverse events did occur more frequently in fluoxetine-treated patients. The TADS data indicated that the addition of CBT enhanced the safety of depression treatment over medication alone.[51]

Epidemiological and observational data. Whereas the pediatric use of antidepressants had been substantially increasing

TABLE 5. SSRIs and pediatric depression overall relative risk of treatment emergent agitation or hostility by drug in MDD trials[50]

DRUG	RELATIVE RISK (95% CI), MDD TRIALS
Citalopram	1.87 (0.34, 10.13)
Paroxetine	7.69 (1.80, 32.99)
Fluoxetine	1.01 (0.40, 2.55)
Sertraline	2.92 (0.31, 27.83)
Venlafaxine	2.86 (0.78, 10.44)
Mirtazapine	0.52 (0.03, 8.27)
Nefazodone	1.09 (0.53, 2.25)
All drugs	1.79 (1.16, 2.76)

MDD = major depressive disorder
CI = Confidence Interval.

throughout the previous decade, youth suicide rates had been declining. During 1992 to 2001, for example, the overall suicide rate among persons 10 to 19 years of age declined from 6.2 to 4.6 per 100,000 population.[52] Each one-percent increase in antidepressant use was associated with a decrease of 0.23 suicides per 100,000 adolescents per year.[53,54] A review of National Vital Statistics from the Centers for Disease Control and Prevention analyzed records of all US individuals at the county level who committed suicide between 1996 and 1998, examining the association between antidepressant prescription and suicide rate.[55] The data demonstrated lower suicide rates in association with increased use of SSRIs and new-generation non-SSRIs, compared to TCA use. A study of suicide in more than 5,000 adults found that, most often, antidepressants had not been taken immediately before death, even though the majority of the persons had been depressed. A study of 14,857 suicides and 26,422 other deaths in Sweden found that none of the 15 suicides below the age of 15 years had an SSRI detected on toxicology.[56] In a study of 49 adolescent suicides in Utah, 24 percent had been prescribed antidepressants, but none had tested positive for SSRIs at the time of death.[57] Most postmortem studies in adults have found that more than 80 percent of depressed patients at the time of suicide are not on antidepressants.[58]

In October 2003, the FDA issued a public health advisory or "black box" warning about the risk of suicidality in pediatric patients taking SSRIs. From 1999 to 2004, pediatric diagnoses of depression increased from 3 to 5 per 1,000. After the FDA advisory, the rates decreased back to 1999 levels, a trend which deviated from historical patterns. Most of the reduction was accounted for by a decrease in depressive diagnoses made by primary care physicians. Among youth diagnosed with depression, the proportion who received no antidepressants increased to three times the rate predicted by the preadvisory trend. SSRI prescription rates were 58-percent lower than predicted by preadvisory trends. However, there was no evidence of any increase in the use of nonantidepressant treatment alternatives. In sum, the advisory was associated with significant reductions in the rates of diagnosis and treatment of pediatric depression. In the US, suicide rates among youth 19 years and younger, increased 18.2 percent between 2003 and 2004, the first significant rise in teen suicide in more than a decade and the largest one-year change in suicide rate in a quarter century.[52]

Risk of nontreatment. While considering the potential risks and benefits of treatment, it is also important to reflect on the risk of not treating MDD. Suicide is the third-leading cause of death among adolescents 15 to 19 years of age, and fourth-leading cause of death among 10 to 14 year olds.[3] One study, which followed depressed pediatric subjects into adulthood, demonstrated a suicide risk of 2.45 percent, with 44.3 percent of the sample attempting suicide at least once in their lives.[32] Other studies have also demonstrated an elevated risk of suicide and psychiatric comorbidity in long-term follow-up studies of depression.[11,19,23] During a period spanning 10 years between adolescence and early adulthood, one group of researchers estimated a five-fold increased likelihood of suicide attempts associated with pediatric depression as well as a high rate of completed suicide (7.7%).[7] Prepubertal children with an earlier age of MDD onset are also at increased risk for substance abuse, conduct disorder, impaired functioning, and need for long-term psychiatric and medical services.[5] Since the "black box" warning issued by the FDA in October 2004, prescription rates for SSRIs have fallen dramatically while concurrently youth suicides have significantly increased.[54]

Summary of risk-benefit analysis of pharmacologic treatment. Analyses of suicidality adverse events collected in the pediatric antidepressant trials have demonstrated an elevation in suicidality when placebo was compared to active medication.[38] Systematic and repeated assessments of suicidality using symptom rating scales, however, have not supported this finding.[59] In fact, when these data were collected in TADS at baseline, 6 weeks, and 12 weeks, all four treatment groups demonstrated a decline in suicidality, with the greatest decline

occurring in the group receiving fluoxetine with CBT. Also of interest are the epidemiological and observational data, which demonstrate an increase in the use of SSRIs in the pediatric population but no corresponding increase in completed suicides.[60] In fact, studies have generally identified an inverse correlation, both nationally and regionally, with suicide and antidepressant usage.

PSYCHOSOCIAL TREATMENTS

CBT. *CBT* is an umbrella term for a number of psychotherapeutic strategies based on the assumption that depression is caused or maintained by negative and distorted cognitions and dysfunctional behaviors. The theoretical framework for CBT maintains that thoughts, feelings, and behavior are interrelated. Treatment is generally here-and-now focused and often includes teaching psychosocial and relaxation skills in addition to the analysis of cognition and behavior. CBT for depression is based on the presumption that depressive symptoms will decrease through interventions that modify dysfunctional thought and behavior patterns. Meta-analyses of randomized, controlled trials of CBT for depressed adolescents have concluded that there is strong evidence supporting efficacy of CBT to treat pediatric depression,[61–63] with effect sizes generally in the moderate to large range, ranging from 1.02 to 1.27, at the end of the acute treatment Additionally, higher rates of remission from depression have been associated with CBT[64] compared to other types of psychotherapy. There is also data suggesting that CBT has a protective effect against suicide attempts in teens.[65]

Several groups have directly compared CBT to other forms of psychotherapy.[66,67] These studies have consistently demonstrated superiority of CBT over other forms of treatment, which have included supportive therapy, relaxation training, and family therapy. Studies that have examined CBT delivered in group format have shown comparable efficacy to CBT administered individually. A meta-analysis of psychotherapy in general for child and adolescent depression revealed a modest mean effect size of 0.34, suggesting that perhaps noncognitive treatments have effects less robust than cognitive treatments.

TADS compared CBT with medication. At the end of the 12-week, blinded, acute phase, CBT alone was less effective than fluoxetine but CBT and fluoxetine alone were equivalent at 18 and at 36 weeks. A combination of medication and CBT performed best at all three time intervals.[51] In this study, medication appeared to accelerate the treatment response, with the addition of CBT enhancing the overall efficacy of the treatment over time as well as to the safety of the patients. Possible explanations for the relatively poor early showing of CBT in TADS is the high severity of psychopathology in subjects and the fact that comorbid DD was nearly three times higher in the CBT-alone group than in the fluoxetine-alone group. Other explanations are that the CBT was highly structured and mainly emphasized skill acquisition, whereas in previous studies the treatments were more flexible and emphasized behavioral changes and cognitive restructuring to a greater degree. Finally, CBT outcomes varied significantly between sites, with the site responsible for developing the CBT manuals experiencing the most success, perhaps suggesting inconsistent levels of therapist expertise among sites.

Interpersonal psychotherapy for adolescents (IPT-A). IPT-A is a psychotherapeutic intervention developed for depressed teens based on a well-established, time-limited, focused treatment for depressed nonbipolar adult outpatients. A central tenet of IPT-A is that clinical depression occurs in an interpersonal context and that response to treatment is influenced by the interpersonal relations between the patient and significant others. The goals of IPT-A are to reduce depressive symptoms and improve interpersonal functioning. IPT-A has been noted to be efficacious in the acute treatment of depressed adolescents in several controlled trials.[68,69] There is evidence of the maintenance of improvement at one year follow up, with associated reduction in hospitalization rates and suicidality.[70]

A recent effectiveness study has compared IPT-A with treatment as usual in the school-based health clinics in New York City as delivered by the clinicians employed in school-based clinics.[71] Treatment as usual consisted of the psychological treatment the adolescents would have received had the study not been in place (generally supportive, individual counseling). Adolescents treated with IPT-A compared with treatment as usual showed greater symptom reduction, significantly better social functioning, and greater decrease in clinical severity of depression and improvement in overall functioning. In addition, the study demonstrated the ability to train community clinicians to deliver IPT-A effectively, thereby demonstrating the transportability of IPT-A from the university lab setting to the community.[35]

IPT-A also has been adapted to a group format (IPT-AG). Mufson et al[72] recently completed a pilot, controlled, clinical trial demonstrating the feasibility and efficacy of IPT-AG for the treatment of adolescents with depressive disorders. Group IPT-AG offers the potential for increasing access while simultaneously optimizing utilization of resources and cost effectiveness.

Family therapy. Few family-based therapies exist for adolescent depression, and their results are inconsistent. One research group reported that children who participated in monthly family meetings as an adjunctive to their individual CBT had a greater reduction in depressive symptoms,

compared with the control group.[73] Other research has demonstrated that an adjunctive multifamily psychoeducation group for families of children with mood disorders increased knowledge, improved family relations, increased child-perceived support from the parents, and increased treatment adherence.[74] Family psychoeducation has been shown to have positive effects on family interactions, which have been postulated to mediate the clinical course of MDD in youth.[75] In contrast, other authors have found no additional benefits to adding a parent-training group to a CBT skills-training group for adolescents.[67] Systemic behavioral family therapy was no better than supportive therapy in reducing depression symptoms in pediatric patients.

Treatment of suicidal behavior and ideation. CBT and dialectical behavioral therapy (DBT) have been found to be effective in reducing suicide attempts among adults.[76,77] Until recently, suicidal adolescents have been excluded from clinical trials. Even when suicidal adolescents were included in samples, few of the studies assessed suicidal ideation and behavior as an outcome.

One group of researchers found that permitting adolescents to immediately rehospitalize themselves if needed was not associated with a significant reduction in suicide attempts at one-year follow up.[78] Other research compared adolescent suicide attempters treated with brief cognitive-behavioral family therapy, either alone or in combination with a emergency room intervention designed to increase adherence.[79] The combination of the family and emergency room intervention resulted in lower rates of depression and suicidality, as well as improved adherence, lower maternal depression, and improved family interaction compared with the family-intervention alone.

In one large-scale study of depressed adolescents, 35 to 40 percent of teens had significant suicidal ideation with a plan or a recent attempt at intake across the three treatments (individual CBT, family therapy, supportive therapy).[65] A substantial reduction in suicidal ideation occurred across the three treatments but there was no differential reduction by treatment.

In TADS, 29 percent of the depressed subjects had clinically significant suicidal ideation upon study entry.[59] Combined treatment (fluoxetine and CBT) was found to be superior to both monotherapies and to placebo in treating depression, whereas neither monotherapy was different from the other or from placebo in reducing suicidal ideation.

CASE VIGNETTE, CONTINUED

Julia and her mother chose to begin antidepressant medication along with CBT-focused psychotherapy. They also agreed to have some additional family therapy sessions in order to improve their relationship and the way they communicate with each other. As Julia began to feel better, she stopped using alcohol and marijuana. Concerned about the rest of the family, Julia's mother asked whether there are ways to prevent depression.

CONCLUSION

Depression and suicidality in youth are significant public health issues. Prevention strategies targeting at-risk youth have demonstrated greater success than interventions applied universally, suggesting a role for routine screening of depression in primary care settings. Fluoxetine and, most recently, escitalopram have accumulated adequate efficacy and safety data to merit FDA-approved indication for the treatment of pediatric depression. The psychotherapeutic treatments shown to be most effective for adolescent depression include CBT and IPT-A. While there have been few empirical studies on the treatment of suicidal behavior among adolescents, the current data suggest that reduced suicidality is associated with successful treatment of depression. When contemplating the risks and benefits of the various treatments, one must also consider the risks on nontreatment, which are likely to be substantial.

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