

Major depressive disorder in children and adolescents

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Abstract

Major depressive disorder (MDD) is one of the most common psychiatric disorders of childhood and adolescence, but because of symptom variation from the adult criteria, it is often unrecognized and untreated. Symptom severity predicts the initial mode of treatment ranging from psychotherapy to medications to combination treatment. Several studies have assessed the efficacy of treatment in children and adolescents, and others have evaluated the risk of developing adverse effects and/or new or worsening suicidal thoughts and behaviors. Optimal treatment often includes a combination of therapy and antidepressant medication. The most studied combination includes fluoxetine with cognitive behavioral therapy. Once symptom remission is obtained, treatment should be continued for 6 to 12 months before a slow taper is initiated. Although most children and adolescents recover from their first depressive episode, a large number will continue to present with MDD in adulthood. Untreated depression in children and adolescents may increase the risk of substance abuse; poor work, academic, and social functioning; and risk of suicidal behaviors.

Keywords: depression, pediatric, child, adolescent, antidepressant, psychotherapy

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Introduction

Major depressive disorder (MDD) can have significant effects when onset occurs in childhood and adolescence. Impaired school performance, interpersonal difficulties later in life, early parenthood, and increased risk of other mental health disorders and substance use disorders have been associated with the diagnosis of MDD in childhood.^{1,2} The rate of depression increases from childhood through adolescence and into adulthood.³ In 2016, an estimated 12.8% of the US population aged 12-17 years

had been diagnosed with at least one major depressive episode.⁴ As many as 8% of adolescents diagnosed with MDD have completed suicide by young adulthood, making suicide the second leading cause of death among adolescents 12-17 years of age.^{3,5}

Early intervention is the key to treatment of depressed youths. Treatment for pediatric MDD includes psychotherapy and antidepressant medications, specifically selective serotonin reuptake inhibitors (SSRIs). Although the risk of suicidality may increase upon initiation of antidepressants, the risk also increases with untreated depression. In addition, depression in adolescence is a risk factor for the suicide, substance use disorders, and long-term psychosocial impairment in adulthood to name a few.^{2,6}

Symptom Presentation

A mother brought her 7-year-old child to the pediatrician concerned her child is no longer playing with toys or riding bikes around the neighborhood with friends. Over the past 3 weeks, the child has been more isolative and increasingly irritable with

Take Home Points

1. Major depressive disorder in children and adolescents is underdiagnosed. Symptom presentation varies from more somatic symptoms and less verbalization of feelings in preschoolers to more verbalization of feelings and symptoms similar to adults in older adolescents.
2. Treatment options for pediatric major depressive disorder should relate to the level of depression severity. First-line treatment is often psychotherapy for mild-to-moderate depression followed by antidepressants for moderate-to-severe depression.
3. In depressed youth, predictors of suicide include baseline suicidality or self-injury, previous suicide attempt, poor family functioning or history of family conflict, use of drugs and alcohol, history of abuse, and female sex. Untreated depression and antidepressant medications may increase the risk of suicidal thoughts and behaviors.

no known trigger, complained of several headaches and stomachaches over the past several weeks, and fears everyone in the family is going to die. Teachers have noted inattention and some impulsive behavior in the classroom. There have also been random periods of uncontrollable crying and screaming without a trigger. There is no history of psychotropic medication, trauma, recent losses, or changes in daily life.

Pediatric MDD is often underdiagnosed and undertreated with only 50% of adolescents diagnosed before reaching adulthood.^{2,7} It is a common, chronic, recurrent, and debilitating disease state, resulting in impairment in educational, occupational, and social functioning.² Up to one third of adolescents who present to their primary care physician may present with an emotional disturbance, and 14% may screen positive for depression.⁸ The Centers for Disease Control and Prevention estimate the incidence at 0.5% in children 3-5 years old, 2% for 6- to 11-year-olds, and up to 12% for 12- to 17-year-olds.³ During childhood, the diagnosis in males and females is equal; however, after puberty, females are more frequently diagnosed with depression. The difference is likely multifactorial; however, females appear to experience more exogenous risk factors for depression prior to and during puberty.⁹

Pediatric depression has been observed in preschoolers as young as 3 years of age; however, children are often less likely to verbalize their feelings or meet the

Diagnostic and Statistical Manual for Mental Disorders (DSM-5) MDD criteria. Depressed children 3-8 years of age often present with more somatic complaints, are more irritable, display fewer signs of depression, present with symptoms of anxiety, and have other problem behavior as listed in Table 1.¹⁰ As children become adolescents and then adults, symptom presentation becomes more consistent with the DSM-5 criteria (Table 1). In addition, youth present with less hypersomnia, more variations in weight and appetite, and fewer delusions compared with adults.¹⁰ Teens may present with fewer complaints of decreased energy or psychomotor slowing compared with adults.⁹ The most common comorbidities include attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, disruptive disorders, substance use disorders, enuresis/encopresis, and separation anxiety disorders.^{2,11}

Left untreated, a major depressive episode often improves and remits within 7 to 9 months of symptom onset; however, children and adolescents who have recovered after treatment often have recurrence within 2 years with 70% incidence by year 5.^{10,12} Although no single variable has been shown to predict the recurrence of MDD in the pediatric population, earlier age of onset, number of depressive episodes, severity of episodes, psychosocial stressors, and comorbid dysthymia may play a role in predicting relapse.^{13,14} Youth often recover from their index episode faster, have a higher rate of recurrence, and have a high propensity for an early switch to bipolar disorder compared with adults.^{2,11}

This case illustrates the difficulty of diagnosing a child with MDD. Without obtaining information from multiple sources, there are features of the child's presentation that could be considered consistent with being bullied or other conditions, such as ADHD, disruptive mood dysregulation disorder, or conduct disorder. When information from parents and teachers are considered together, symptoms of depression include frequent somatic complaints, unexplained irritability, crying, shouting, anhedonia, and isolation. This child presents with a fear of death for family, which is often observed in older children. The usual adult symptoms are not depicted in this case as is typical in pediatric depression. In addition, it is important to obtain collateral information about daily functioning or mood changes from parents, guardians, caregivers, and teachers to aid in diagnosis because children may have poor insight regarding their symptoms. Rating scales, such as the Children's Depression Rating Scale-Revised (CDRS-R) and Children's Depression Inventory, should be used by clinicians to aid in diagnosis.^{2,7}

TABLE 1: Clinical presentation variation compared to adult symptom onset for major depressive disorder¹⁰

Age, y	Clinical Presentation Variation
3-5	Trouble verbalizing feelings, marked decreased interest in play, self-destructive themes in play, thoughts of worthlessness or suicide, symptoms do not need to be present for 2 wk
6-8	Trouble verbalizing feelings, increased somatic complaints, crying or shouting outbursts, unexplained irritability, observed anhedonia
9-12	Low self-esteem, guilt, hopelessness, increased boredom, feelings of wanting to run away, and fear of death
13-18	Increased irritability, impulsivity, and behavior changes; decreased grades and poor school performance; increased disturbances in sleep and appetite; suicidality similar to adults; increased likelihood of chronic course of depression; stronger genetic association
≥19	Symptoms similar to adult presentation

Treatment Options for Pediatric Depression

A 15-year-old with a history of MDD receiving cognitive behavioral therapy (CBT) for the past 3 months and fluoxetine 60 mg daily for 4 weeks (titrated from 10 mg daily over 10 weeks) continues to exhibit symptoms of low mood, anhedonia, poor sleep onset, and declining grades. The patient has not been able to reestablish relationships with friends and feels there is no longer any point in living or attending college, which is a change since the last fluoxetine increase. Self-injurious behavior, including cutting bilateral forearms and hips “as a way to not feel numb,” is a daily occurrence. The patient denies any adverse effects from fluoxetine and has never tried any other antidepressant medication.

Psychoeducation and Psychotherapy

Treatment options for depressive disorder in children and adolescents vary by severity similar to adult treatment. Mild-to-moderate depression may be managed with psychoeducation, family education, and psychotherapy, and more severe depressive episodes may require pharmacotherapy.

Psychoeducation is important for both the patient and family, so everyone is aware of the treatment plan and goals. When education is provided, treatment adherence increases. Psychoeducation may include signs and symptoms of depression, clinical course of illness, risk of recurrence, treatment options, and advice for parents on interacting with their depressed youth.¹³

Psychotherapy options include but are not limited to individual or group CBT or interpersonal psychotherapy (IPT).¹ Both have been shown to be effective for adolescents but none more effective than the other.¹⁵ For mild cases of MDD, psychotherapy is effective for 62% of individuals.¹⁶ A meta-analysis demonstrated a signifi-

cant but modest effect size for psychotherapy for MDD in 8- to 19-year-olds.¹⁷ A randomized clinical trial comparing IPT for depressed adolescents (IPT-A) to treatment as usual (supportive counseling in a school-based clinic) in adolescents 12-18 years of age with depression demonstrated IPT-A significantly reduced depressive symptoms on the Hamilton Depression Rating Scale over a 12-week period compared to treatment as usual ($P < .001$).¹⁸ No studies have been conducted comparing IPT-A to pharmacotherapy.

Pharmacotherapy

Antidepressant medications may be considered first-line treatment for moderate-to-severe depression or depression that has not responded to an adequate trial of psychotherapy.^{15,19,20} Medications should not be the only form of treatment for depressed pediatric patients, but used in combination with psychotherapy. In clinical practice, both treatment modalities are often initiated during an acute-care hospitalization, particularly if admission is for suicidal ideation or attempt.

Selective serotonin reuptake inhibitors are the first-line antidepressant agents for children and adolescents diagnosed with depression. Fluoxetine is approved by the Food and Drug Administration (FDA) for children 8 years of age and older, and escitalopram is approved for ages 12 years and older. Fluoxetine has the strongest evidence for use in pediatric depression, including 4 positive randomized, controlled trials.²¹ Two recent meta-analyses have noted a small therapeutic effect for all antidepressants with fluoxetine being the only antidepressant to have a statistically significant effect over placebo on efficacy for the treatment of depression.^{22,23}

The pivotal Treatment of Adolescent Depression Study (TADS) compared fluoxetine, CBT, fluoxetine + CBT (combination treatment), and medication placebo in 439 adolescents with moderate-to-severe depression.⁶ At the end of the 12-week acute phase, combination treatment was superior to fluoxetine monotherapy ($P = .02$) and CBT

alone ($P=.01$) based on the CDRS-R scores.⁶ Fluoxetine monotherapy was superior to CBT alone ($P=.01$) at the end of the acute phase.⁶ Based on the scores of the Clinical Global Impressions–Improvement (CGI-I) scale, rates of response (score 1 = “very much improved” or 2 = “much improved”) were as follows: 71% for combined treatment, 61% for fluoxetine monotherapy, 43% for CBT alone, and 35% for placebo. Faster onset of improvement and time to stabilization was observed for combination treatment and fluoxetine monotherapy compared with placebo ($P=.001$).⁶ At week 36, all active treatments converged on remission outcomes; however, combination treatment remained the most cost-effective.^{24,25} At 1-year follow-up, benefits of treatment had continued for depression and suicide measures based on CDRS-R scores and self-reported depression and suicide scores.²⁶

The Treatment of Resistant Depression in Adolescents (TORDIA) study examined the use of a second SSRI or venlafaxine with or without CBT in 334 adolescents who failed to respond to an initial SSRI trial.²⁷ Similar to the TADS trial, response rates on the CGI-I scores demonstrated combination treatment was superior to medication monotherapy (54.8% vs 40.5%, $P=.009$).²⁷ No difference in response rates was observed between a second SSRI versus venlafaxine ($P=.83$).²⁷ In addition, no significant difference in adverse effects between any treatment group was observed.²⁷

The Adolescent Depression Antidepressant and Psychotherapy Trial assessed subjects 11–17 years of age with moderate-to-severe depression who did not respond to brief initial psychosocial intervention. At the end of 12 and 28 weeks, SSRIs plus CBT did not provide any additional benefit over SSRIs alone. Of note, 21% of participants did not respond by week 28 to either treatment, SSRI or SSRI plus CBT.²⁸

Other SSRIs; serotonin norepinephrine reuptake inhibitors (SNRIs); and other antidepressants, such as mirtazapine and bupropion should be prescribed but with caution because of the paucity of robust and high-quality evidence that is available.^{2,23} Despite the lack of data, the benefit of treatment outweighs the risk of harm 6 to 1.²⁹ In a recent meta-analysis compared with placebo, fluoxetine, sertraline, and escitalopram demonstrated statistical significance on efficacy outcomes using multiple rating scales; however, the quality of studies was low and, therefore, difficult to interpret and generalize to the pediatric population.^{22,30}

When considering antidepressants for pediatric patients, choice should be based on depression severity, timing of therapeutic effect, danger of overdose, adverse effect profile, drug interactions due to inhibition of cytochrome, patient and guardian preference, and comorbidities.^{2,13}

For example, fluoxetine may be more favorable for a patient with a history of intermittent missed doses because of its longer half-life; however, it requires longer to achieve steady state than other antidepressant medications. Certain antidepressants carry the risk of drug interactions due to inhibition cytochrome P450 1A2 (fluvoxamine), 2D6 (fluoxetine, paroxetine, duloxetine, bupropion), and 3A4 (fluvoxamine). These agents should be prescribed with caution and titrated slowly in patients concurrently taking substrates of these enzymes.^{2,31} Bupropion may also be beneficial for patients with comorbid ADHD or a tobacco use disorder. Paroxetine is useful for severe anxiety but carries the risk of increased suicidality compared with other SSRIs and increased sedation in the pediatric and young adult population.¹⁰ Mirtazapine is beneficial for patients with sleep disturbances but may also cause weight gain, which is often a deterrent for some adolescents.³² Selective serotonin reuptake inhibitors have an increased risk of behavioral disinhibition or activation when prescribed for children, especially preschoolers compared with adolescents and adults.^{32,33} Tricyclic antidepressants and monoamine oxidase inhibitors should be reserved for treatment refractory depression due to limited efficacy, increased risk of adverse effects, and potential lethality in overdose.³³

Medications should be initiated at low doses, lower than adult starting doses when possible, and increased every 1 to 2 weeks until therapeutic effect or adverse effects occur.^{2,34} Frequency and timing of doses should be considered to limit frequency and avoid administration at school. Some formulations of bupropion and fluvoxamine require multiple daily dosing, which may be a deterrent for some children and parents. Children and adolescents may be at increased risk of developing antidepressant withdrawal symptoms compared with adults, but less risk is associated with fluoxetine because of its long half-life.^{2,34} It is important to stress the need for adherence with medications. Prior to initiation, patients and guardians should be informed about the risk of adverse effects, the possibility of inducing mania or behavioral activation/disinhibition, potential for reduced height and weight compared with same-age peers, and the risk of worsening suicidal thoughts or behaviors.^{2,32,34} The exact duration of an antidepressant trial in youth has not been established; however, the general consensus is, once symptoms have resolved, the medication should be continued for 6 to 12 months before initiating a slow taper off the medication.¹ Medication discontinuation should occur during periods of low stress, such as summer vacation.¹

Despite the limited evidence, augmenting agents for pediatric patients often include lithium; bupropion; and second-generation antipsychotics, such as quetiapine.³³

TABLE 2: Select antidepressant dosing and adverse effects^{1,10,13,20,34}

	Starting Dose	Effective Dose, mg	Maximum Dose, mg
Selective serotonin reuptake inhibitors			
Citalopram	10 mg/d	20	40
Escitalopram ^a	5 mg/d	10-20	20
Fluoxetine ^b	5-10 mg/d	10	40
Fluvoxamine	25 mg/d	150	300
Paroxetine ^c	10 mg/d	10	20
Sertraline	25 mg/d	50	200
Serotonin norepinephrine reuptake inhibitors			
Duloxetine	20-30 mg/d	30-60	60
Venlafaxine	12.5-25 mg/d	37.5-75	150-225
Miscellaneous agents			
Bupropion	75 mg/d	75-150	150-300
Mirtazapine	15 mg/night	15-30	15-45

^aFood and Drug Administration approved for depression in adolescents 12-17 years of age.

^bFood and Drug Administration approved for depression in children and adolescents 8-17 years of age.

^cShould be avoided in youth due to increased risk of suicidality compared with other antidepressants.

When combined with imipramine after nonresponse to 6 weeks of treatment, lithium did not significantly improve depression symptoms.³⁵ When combined with any tricyclic antidepressant after nonresponse to 4 weeks of treatment, about 40% of patients responded to lithium augmentation.³⁶ In a small case series (n=10), 70% of participants responded to quetiapine augmentation when SSRI treatment was ineffective.³⁷

Repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) are other options for treatment when therapy and medications are ineffective. Electroconvulsive therapy should only be considered for chronic, severe, disabling depression after nonresponse to at least 2 adequate trials of antidepressants.³⁸ A second opinion from a child-and-adolescent psychiatrist is recommended prior to initiating the steps to begin the ECT process. No randomized, controlled trials of rTMS or ECT in pediatric patients have been conducted (Table 2).³³

Types of antidepressant adverse effects (ADEs) are similar in children and adults. Compared with adults, children and adolescents are at increased risk of behavioral activation/disinhibition (restlessness, jitteriness, hyperactivity), hypomania or mania, decreased height and weight, and new-onset suicidal thoughts or behaviors.^{2,32,34} Bupropion may cause less sexual dysfunction, which may be important to consider for older adolescents (Table 3).³²

This section's case illustrates the need for the next steps in treatment of a 15-year-old who has not responded to the combination of psychotherapy and pharmacotherapy. The patient appears to have responded minimally to both treatment modalities

with a possible increase in passive suicidal thoughts. At this time, a change of antidepressant is appropriate. In clinical practice, the suggestion would be to change to another SSRI, such as escitalopram or sertraline, or an SNRI, such as venlafaxine, by a cross-taper and titration strategy to prevent further symptom decompensation.^{13,20,27,38} A partial response to a second antidepressant may warrant the consideration of an augmentation strategy with either lithium or quetiapine.^{13,20,27,38} Electroconvulsive therapy and rTMS would only be considered if depression remains resistant to medication and therapy after 2 adequate trials.^{38,39} Should symptoms continue to respond poorly to MDD treatment, a reconceptualization of the diagnosis or a multidisciplinary review should be considered as symptom overlap and evolution can happen as an individual moves from childhood to adolescence to adulthood.^{2,15}

Suicide

A 13-year-old was recently diagnosed with MDD and initiated treatment with escitalopram 10 mg daily with IPT-A. For the past 3 days, symptoms include new thoughts about self-harm and no longer wanting to live. Recent suicidal ideation includes thoughts of overdosing on grandfather's pain medication or walking into traffic. Parents have been taking turns sleeping in the room to ensure safety at night and have locked up all medications and sharps at home. Despite 2 previous attempts, the patient denies intent, stating "I do not want to cause my family pain." The 2 previous attempts include ingesting a mouthful of bleach after an

TABLE 3: General treatment guidelines^{15,19,34}

Stages of Treatment	Severity of Depression	Treatment Recommendations
1	Mild to moderate	Cognitive behavioral therapy Interpersonal psychotherapy-adolescents Acceptance and commitment therapy Mindfulness-based cognitive therapy Family interventions
	Moderate to severe	First-line Selective serotonin reuptake inhibitors Serotonin norepinephrine reuptake inhibitors Norepinephrine dopamine reuptake inhibitor Noradrenaline and specific serotonergic antidepressant Second-line Tricyclic antidepressants Monoamine oxidase inhibitors
2		Combination therapy (medication + therapy) Increase antidepressant dose Augment antidepressant with lithium ± antipsychotic Antidepressant combination Repetitive transcranial magnetic stimulation
3		Electroconvulsive therapy

argument with mom (2 years ago) and cutting wrists severely enough to require stitches (2 weeks ago). Parents are currently divorcing but are still living in the same house and avoid speaking to each other.

Suicide is the second leading cause of death in adolescents in the United States. About 90% of adolescents who commit suicide have been diagnosed with a psychiatric disorder.⁴⁰ The single most common diagnosis is MDD, which presents in 35% of suicidal adolescents.⁴⁰ Nationwide, 15.8% of youth have seriously considered suicide with the rate being higher for females (19.3%) than males (12.5%).³ For individuals ages 10-19 years, the overall suicide rate was 4.5 suicides per 100 000 persons based on the 2010 National Vital Statistics System.³ The rates were higher among boys than girls and older children (15-19 years) than younger children (10-14 years).³

A meta-analysis of 24 studies revealed an increased risk of suicidal behavior or ideation for those receiving medication compared with placebo (4% vs 2%).⁴¹ In 2004, the FDA added a black box warning to all antidepressants warning of the increased risk of suicidal thoughts and behaviors for children, adolescents, and young adults. Following the issuance of the warning but despite the continued diagnosis of depression, the prescribing of SSRIs in adolescents decreased, particularly for youth 14 years of age and younger.⁴² In addition, the rate of suicide increased by 14% in the United States from 2003 to 2004, which was the largest annual increase since 1979.⁴²

Between 1992 and 2001, each 1% increase in adolescent antidepressant prescribing was associated with a decrease of 0.23 suicides per 100 000 adolescents per year.⁴³

Several studies have assessed the association of suicide with antidepressant use. The most notable are the TADS, TORDIA, and the Treatment of Adolescent Suicide Attempters (TASA) trials.^{6,27,44} Comparison of the studies for the risk of suicide can be difficult because the definitions of suicide, suicide attempts, and self-injurious behavior can vary along with the time frame used to assess such events. In addition, each of the studies assesses different treatment modalities, potential baseline causes associated with suicidal attempts and behaviors, and age groups. When prescribing antidepressants in youth based on the FDA recommendations, baseline assessment of suicidality and self-injury is advised along with close observation and monitoring for changes in behavior, clinical worsening of symptoms, or suicidality.³⁴ Questionnaires, such as the Suicidal Ideation Questionnaire–Junior High School Version or the Columbia Suicide History Form may be used to assist with monitoring of suicidality.^{6,44}

The TADS study demonstrated a decline in suicidal events during the acute phase for all 4 treatment groups.⁶ Suicidal events were defined as worsening suicidal ideation or attempt or both. Forty-four events were documented at the end of the 36-week follow-up period with the following rates for each treatment group: 14.7% for fluoxetine only, 10% for placebo, 8.4% for the

combined treatment group, and 6.3% for psychotherapy. For suicidality, fluoxetine with CBT was statistically superior to all other treatment groups during the acute phase; however, fluoxetine alone was not statistically superior to any other treatment.⁶ The rate of suicidal events was higher during the acute phase than the follow-up period (61.4% vs 38.6%).^{6,24}

In the TORDIA trial, there was no advantage of combined treatment over medication alone on the rate of suicidality; however, 14% of subjects had a suicidal event over 12 weeks of follow-up, and 9% had a nonsuicidal self-injury event.²⁷ The median time to a suicidal event was 3 weeks.²⁷ Of note, if suicidal ideation was present at baseline, then venlafaxine was associated with a higher rate of self-harming behaviors.²⁷

The goal of the TASA study was to identify the predictors of suicide events and attempts in depressed suicide attempters 12-18 years of age.⁴⁴ Median time to suicidal event was 44 days with 40% occurring within 4 weeks of treatment initiation.⁴⁴ The event occurrence was predicted by higher self-rated severity of depression, increased number of previous suicide attempts, earlier time to suicidal event, lower lethality of previous attempts, history of sexual abuse, and familial conflicts.⁴⁴

Based on results from a meta-analysis evaluating the effects of IPT for youth 6-18 years of age with MDD, IPT produces a slight but not statistically significant decrease in suicide risk. There are no current studies that evaluate the effects of IPT-A on suicidality.⁴⁵

This case demonstrates the increased risk of suicidality with the initiation of antidepressant medications and the need to consider a change in antidepressant medication. It also illustrates some risk factors that are predictive of suicide, including female sex, baseline self-injury, increased number of previous suicide attempts, and history of family conflict. Because baseline suicidal ideation is present, venlafaxine would not be an appropriate next medication for this patient. Although all antidepressants have the black box warning for increased suicidal thoughts and behaviors with new starts or dose changes, not every antidepressant will have the same effect on the same individual. Fluoxetine or another SSRI would be an appropriate alternative for this patient. Therapy should also be continued while the medication is changed and adjusted.

Summary

Depression may affect up to 12% of youth; however, because symptom presentation may vary from adult characteristics, it goes under-recognized and undertreat-

ed. Consequences of untreated depression include impaired school performance and social functioning and increased risk of suicidal ideation and attempts. Initial treatment of mild depression includes psychotherapy, and moderate-to-severe MDD may include a combination of psychotherapy and medication. With children and adolescents, there is an increased risk of adverse effects, including the increased risk of suicidality. Proper monitoring includes close observation for changes in behavior and suicidal thoughts and behaviors with the initiation of these medications to assess for the development of ADEs and worsening suicidality. The FDA no longer recommends a specific time frame for monitoring; however, follow-up evaluation in 4 to 6 weeks, if not sooner, is suggested in clinical practice.

Suicidality is a common comorbidity with MDD in children and adolescents. Predictors of suicide include previous suicide attempt and poor family functioning. The benefits of using medication to manage a depressive episode in pediatric patients must be weighed against the risk of developing suicidality, if not already present, or worsening it versus the ability of parents/guardians and mental health clinicians to monitor the patient's symptomatology. In the end, psychotherapy plus medication is often the recommended treatment approach for MDD in children and adolescents with monitoring for increased risk of suicidality and ADEs, including a switch to hypomania/mania.

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