Mood and Affect Disorders

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Educational Gap

Major depressive episodes are common, with a reported incidence by age 17 years as high as 18.2% for girls and 7.7% for boys. Pediatricians should play a critical role in the diagnosis, triage, and treatment of children with mood and affect disorders.

Objectives After completing this article, readers should be able to

1. Understand that depressive and bipolar disorders are common.
2. Know the differential diagnosis of depressive disorders.
3. Be able to screen and assess for suicidal risk.
4. Describe the role pediatricians play in the management of depressive and bipolar disorders.
5. Know the basic pharmacology for major depressive disorder.

Abstract

Depressive disorders are common in children and adolescents, with estimates for depressive episodes as high as 18.2% for girls and 7.7% for boys by age 17 years, and are a major cause of morbidity and even mortality. The primary care pediatrician should be able to (1) diagnose depressive disorders and use standardized instruments; (2) ask about suicide, self-harm, homicide, substance use, mania, and psychosis; (3) triage the severity of illness; (4) be aware of the differential diagnosis, including normal development, other depressive disorders, bipolar disorders, and comorbid disorders, such as anxiety and substance use; (5) refer to evidenced-based psychotherapies; (6) prescribe first-line medications; and (7) provide ongoing coordination in a medical home. Pediatric bipolar disorders and the new disruptive mood dysregulation disorder (DMDD) diagnoses are controversial but not uncommon, with prevalence estimates ranging from 0.8% to 4.3% in children at various ages. Although the pediatrician is not likely to be prescribing medications for children with bipolar disorder and DMDD diagnoses, all clinicians should be familiar with common neuroleptics and other mood stabilizers, including important potential adverse effects. Basic management of depressive and bipolar disorders is an important skill for primary care pediatricians.

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
CBT	cognitive behavioral therapy
CES-D	Center for Epidemiologic Studies Depression Scale
DMDD	disruptive mood dysregulation disorder
DSM-5:	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
FDA	Food and Drug Administration
MDD	major depressive disorder
MDE	major depressive episode
SSRI	selective serotonin reuptake inhibitor

CASE EXAMPLE

Jimmy Smith is a 12-year-old boy with a history of attention-deficit/hyperactivity disorder (ADHD) brought to the pediatrician's office by his parents because of poor sleep. Jimmy says he has been averaging 6 hours of sleep a night because he has a hard time falling asleep, and his teachers have commented that he is fatigued during class, leading to declining grades. His mother notes that he often picks at his food and refuses to eat with the family. Although he previously played on the basketball team, he decided not to participate this year. For the past 2 months, Jimmy has been arguing more with his parents, especially after being asked to put away his computer, with 10-minute shouting matches approximately 5 days a week that have never resulted in physically aggressive actions. This is a clear change from his prior behavior. His mother says she had depression, and the paternal grandfather reportedly had bipolar disorder. After discussing the differential diagnosis, his mother asks, "Does Jimmy have bipolar?"

DEFINITIONS

Mood and affect disorders are most frequently defined using the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), released in May 2013. Unlike the prior version that had a single mood disorder category, the *DSM-5* separates depressive disorders (Table 1) and bipolar and related disorders (Table 2) into 2 chapters, with a conceptual aim to place bipolar disorder between the depression and schizophrenia sections. These disorders are based on 3 categories of symptoms: a major depressive episode (MDE), mania (the core feature of bipolar I disorder), and hypomania (the core feature of bipolar II disorder). Several changes to diagnostic criteria for mood disorder diagnoses in *DSM-5* are covered in this article (Table 3), including the creation of the DMDD diagnosis (Table 4). (1)

MAJOR DEPRESSIVE DISORDER

Epidemiology and Pathophysiology

The epidemiology of mental health disorders varies depending on the study, but 2 large national surveys suggest that by age 17 years the lifetime prevalence of a major depressive disorder (MDD) is 12.8% to 15.4%, with a much higher prevalence in girls (15.9%–18.2%) compared with boys (7.7%) and in older children (15.4% in those ages 17–18 years) compared with younger children (8.4% in those ages 13–14 years). The prevalence of an MDE in the past 12 months, based on symptoms reported by a national sample of children ages 12 to 17 years, was 12.0% for girls and 4.5% for boys. (2)(3)

Depression is almost always multifactorial, and most children have a combination of acute and chronic stressors as well as underlying biological, developmental, and psychosocial vulnerabilities. There are clear genetic underpinnings to depression, and the biological correlates to depression are increasingly being understood. For example, functional imaging studies reveal significant differences in emotional processing areas of the brain, such as the medial prefrontal cortex, anterior cingulate, amygdala, and thalamus.

Psychosocial stressors clearly play a role in depression, including epigenetic mechanisms relating to stress hormones. Risk factors include low parental warmth, childhood sexual abuse or parental loss, low educational level, low social support, personality factors, chronic medical illness, prior anxiety and conduct disorders, and substance abuse. Gay, bisexual, lesbian, and transgender youth have also widely been reported to have higher rates of depression and suicidal ideation, although this higher risk appears to be mediated by protective factors, such as family connectedness, presence of caring adults, and safety at school.

Depression is debilitating and is the leading cause of global disability according to the World Health Organization. In adolescents, depression can lead to low self-esteem, academic and social difficulties, and parental stress with lost workplace productivity and directly relates to teenage suicide, which is the second leading cause of death in adolescents ages 12 to 17 years in the United States. (2)

Clinical Aspects

Children and adolescents with depression can present with a variety of somatic, behavioral, and psychological symptoms. Some present with changes in appetite, sleep, or energy, without mention of mood issues unless raised by the astute clinician. Somatic symptoms, including headache, stomachache, and fatigue, are common. Melancholic depression is less common in children than adults, and fewer children or adolescents describe feeling sad or "blue." Many children will present with irritability, conflicts at home or school, acting-out behaviors, or changes in function (eg, declining grades and withdrawal from social circle or activities). As behavioral health screening becomes increasingly implemented in primary care, depression may also arise through instruments such as the Pediatric Symptom Checklist.

With any concerns for depression, pediatricians should obtain a history from the parents. In addition, parents should be asked to step out of the room so the child can be interviewed alone. With the parent absent, it is a good opportunity to review confidentiality; core depressive symptoms; thoughts about suicide, self-harm, or hurting others; substance use; and signs of mania and psychosis (Table 5).

TABLE 1. *DSM-5* Depressive Disorders

Major depressive disorder
Disruptive mood dysregulation disorder
Persistent depressive disorder (dysthymia)
Premenstrual dysphoric disorder
Substance or medication-induced depressive disorder
Depressive disorder due to another medical condition
Other specified depressive disorder
Unspecified depressive disorder

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

The use of specific rating scales, such as the Patient Health Questionnaire 9 (PHQ-9) or the Center for Epidemiologic Studies Depression Scale (CES-D), is highly encouraged. Although these tools should never replace clinical judgment, they can help establish a diagnosis and triage the severity through a validated instrument. (4)(5)

In terms of suicide, both acute and chronic factors should be considered. Acute factors include suicidal ideas, plans, intent, preparation, recent attempts, access to lethal means (especially firearms), current substance use, acute psychosocial stressors, mood symptoms, psychosis, agitation, and impulsivity. Chronic factors include past suicide attempts; a family history of suicide; identifying as gay, bisexual, lesbian, or transgender; personality disorders; and chronic medical illness. Key protective factors include perceiving family and social supports and religious beliefs. If the pediatrician thinks there is significant immediate concern given the acute and chronic risk factors, with minimal protective factors, then the child should be evaluated emergently by a mental health care professional.

TABLE 2. *DSM-5* Bipolar and Related Disorders

Bipolar I disorder
Bipolar II disorder
Cyclothymic disorder
Substance or medication-induced bipolar and related disorder
Bipolar and related disorder due to another medical condition
Other specified bipolar and related disorder
Unspecified bipolar and related disorder

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

For all teenagers, safety planning should include contingencies for worsening suicidality or homicidality, including speaking to a responsible adult before action, contacting an on-call physician, calling 911, or presenting to the nearest emergency department. Parents (and physicians) are sometimes afraid to ask children about thoughts of self-harm. They should be reassured that asking about suicide does *not* increase risk and is, in fact, protective. (6)

Differential Diagnosis

With the exception of substance abuse, it is uncommon for depression to be secondary to a medication or general medical condition. Unless the history or physical examination suggests a concern for thyroid disease or a medication adverse effect (eg, from glucocorticoids), laboratory tests or neuroimaging studies are generally not necessary. For children with significant somatic symptoms, including fatigue, a blood cell count (especially for postmenarchal girls) and thyroid function screening may be reasonable.

The differential diagnosis for MDD is broad, and any child with emotional or behavioral symptoms needs to be evaluated within his or her psychosocial and developmental context. The most common possibility is a developmentally appropriate and limited response to "normal" adverse childhood experiences of grief, loss, or disappointment. Although all children experience sadness and most adolescents will have some degree of irritability and mood lability, MDD is distinguished by the duration, presence with other depressive symptoms, and severity compared with children of the same developmental stage.

TABLE 3. Select Changes in *DSM-5*

Mood disorder section divided into depressive disorders and bipolar and related disorders
Addition of DMDD
Persistent depressive disorder replaced dysthymia and chronic major depressive disorder
Removal of bereavement exclusion for depression
Addition of specifier "with anxious distress" to bipolar or depressive diagnoses for patients with significant symptoms of anxiety
Addition of specifier "with mixed features" to bipolar or depressive diagnoses for patients with features of both mania and depression
Bipolar I and II disorders emphasized changes in energy and activity, in addition to mood
Other specified disorders are created and not otherwise specified diagnoses eliminated

DMDD=disruptive mood dysregulation disorder; *DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

TABLE 4. Summarized Diagnostic Criteria for Disruptive Mood Dysregulation Disorder[a]

A. Severe recurrent temper outbursts manifested verbally and/or behaviorally that are grossly out of proportion in intensity or duration to the situation or provocation
B. The temper outbursts are inconsistent with developmental level
C. The temper outbursts occur, on average, 3 or more times per week
D. The mood between temper outbursts is persistently irritable or angry most of the day nearly every day and is observable by others
E. Criteria A–D have been present for 12 or more months, with no period lasting 3 or more consecutive months without all the symptoms in criteria A–D
F. Criteria A and D are present in at least 2 of 3 settings and are severe in at least 1 of these

[a]*The diagnosis should not be made for the first time before age 6 years or after age 18 years and must have onset before age 10 years. There can be no distinct periods that last more than 1 day consistent with a manic or hypomanic episode, and behaviors cannot occur exclusively during an episode of major depressive disorder. Symptoms cannot be better explained by another mental disorder and are not attributable to the physiologic effects of a substance or to another medical or neurologic condition.*

Other depressive diagnoses are listed in Table 1. In the *DSM-5*, dysthymia and chronic MDD have been consolidated into persistent depressive disorder, which requires a 2-year duration (1 year in children) and only 2 (or more) depressive symptoms. An adjustment disorder requires a specific stressor that started within 3 months before the symptoms; if the symptoms meet the criteria for an MDE, an adjustment disorder diagnosis is not allowed. In previous editions of the *DSM*, major depression could not be diagnosed during a mourning period. In *DSM-5*, this bereavement exclusion has been eliminated, noting that grief is mostly emptiness with intermittent thoughts of the deceased, whereas an MDE is mostly depressed mood and anhedonia with persistent self-critical thoughts.

Once it is determined that a child has depression, the pediatrician must consider whether it is bipolar depression (part of a bipolar disorder) or unipolar depression (without a history of hypomania or mania). Because childhood depression is more frequently irritable than melancholic, the distinction among depression, bipolar disorder, and DMDD is difficult; the presence of irritability concurrent with sadness, crying, hypersomnia, daytime fatigue, anhedonia, low self-esteem, decreased energy, increased weight, and psychomotor retardation can help distinguish a depressive episode from bipolar disorder and DMDD. The *DSM-5*'s new "with mixed features" specifier may allow for subsyndromal classifications.

The clinician should also evaluate for other psychiatric disorders because comorbidities can suggest other treatment strategies and can contribute to a higher-risk depression. Anxiety disorders, such as generalized anxiety disorder and panic disorders, are common, and subsyndromal anxious symptoms can now be incorporated into the *DSM-5*'s "with anxious distress" specifier. Substance abuse is both commonly comorbid with depression and, in the case of a substance-induced depressive disorder, causative of depression. History can be helpful to distinguish these two—an MDE that preceded substance use and occurs during periods of prolonged sobriety is more likely to be a primary MDD—but in practical clinical care, we often recommend treating both disorders simultaneously.

On the basis of this initial clinical assessment, including with a standardized instrument, the pediatrician should be able to make a preliminary risk stratification of mild, moderate, or severe depression. Although mild depression has fewer symptoms that are less distressing and impairing, and moderate depression has more impairing symptoms, severe depression is characterized by a large number of symptoms, including serious symptoms (such as psychosis or significant safety concerns), major psychosocial stressors, or multiple comorbidities, including substance abuse and anxiety.

TABLE 5. Examples of Must-Ask Questions to Evaluate for Depressive and Bipolar Disorders

Suicide: "Sometimes when I meet teens that are feeling down, they feel like life is not worth living. Has that ever happened to you?"
If so, "Did you ever have thoughts of ending your own life?"
If so, "Did you ever develop a plan? What was it?"
If so, "Did you act on those plans?" and "Have you ever tried to end your life before?"
Self-harm: "Have you ever tried to hurt yourself?" "For example, cutting or burning yourself?"
Homicide: "Have you ever had thoughts about hurting others?"
Substance use: "How often do you drink alcohol? Smoke cigarettes? Use marijuana? Use more medications than prescribed or use other people's pills? How about other drugs like opiates, stimulants, benzos, Molly, cocaine, spice, or others?"
Mania: "Have you ever had a period that you felt super happy or irritable, felt like you had a lot you wanted to do, or had lots of energy?"
Psychosis: "Have you ever felt like your mind was playing tricks on you? Perhaps you saw or heard something and you were not sure whether it was there?"

Management

Primary care pediatricians must play a critical role in managing children with depression as part of a patient-centered medical home and because of the shortage of mental health care professionals in almost all communities, despite the fact that the generalist might feel the need to seek additional training in taking care of these patients. As described in a recent review on quality indicators for adolescent depression, pediatricians should be involved in screening, diagnosis, and suicide risk assessment and play an active role in communication and documentation, setting up treatment, and, in some cases, tracking the adequacy of treatment, symptom reassessment, and treatment adjustment. (7)

The main treatments for depression are psychotherapies and medications. Psychotherapy is the first-line treatment for mild to moderate depression and, combined with medications, for moderate to severe depression. Both psychotherapies and medications are evidenced-based in large randomized clinical trials, and neuroimaging evidence reveals that treatment changes brain areas affected by depression. Response can be defined as having no symptoms or a significant reduction in depressive symptoms for at least 2 weeks, remission for 2 to 8 weeks with no or few depressive symptoms, and relapse as an MDE during remission. Standardized instruments often have quantitative definitions for both response and remission.

Psychotherapies

For all depression, we recommend support for the child and family, education about depression, and advice about nutrition, exercise, and sleep. Particularly for mild depression, as few as 2 sessions of brief supportive counseling can be sufficient.

Cognitive behavioral therapy (CBT) is a well-established treatment for depression in children and adults. It seeks to restructure distorted negative thinking, encourage active behaviors, teach mood monitoring, and help with goal-setting and problem-solving. It is focused on an individual's thoughts, feelings, and behaviors in the present and deemphasizes family relationships and past experiences. In the Treatment for Adolescents With Depression Study, a randomized clinical trial that compared fluoxetine, CBT, combined treatment, and placebo, after 12 weeks 71.0% achieved a response with combined treatment, 60.6% with fluoxetine alone, 43.2% with CBT alone, and 34.8% with placebo. (8) By 36 weeks of follow-up, response rates were equivalent at 86% with combination treatment, 81% with fluoxetine, and 81% with CBT. (9)

Interpersonal therapy, in contrast to CBT, focuses on a patient's relationships with family and peers, coping with stressors with others, and problem-solving ways to make relationships more positive. Although there is less evidence for family therapy, school-based interventions, individual psychodynamic psychotherapy, and community interventions, in our experience all are important potential therapies, depending on a child's individual situation.

Medications

Medications are indicated to treat moderate to severe depression and mild to moderate depression that has not achieved a response to psychotherapy after 6 to 8 weeks. Large clinical trials, including the Treatment for Adolescents With Depression Study, have revealed the efficacy of antidepressants for adolescent depression. However, as per the Treatment of Resistant Depression in Adolescents trial, only approximately 60% of adolescents respond to an adequate

TABLE 6. **Dosing for the Primary Care Pediatrician of Several Antidepressants**

GENERIC NAME (BRAND NAME)	STARTING DOSE, MG		DOSE INCREASES (ABOUT EVERY 1-2 WEEKS), MG		TYPICAL DOSE RANGE, MG	
	ADOLESCENT	PREADOLESCENT	ADOLESCENT	PREADOLESCENT	ADOLESCENT	PREADOLESCENT
Fluoxetine (Prozac)[a]	10	5	10	5	20–80	10–40
Sertraline (Zoloft)[b]	25	12.5	25	12.5	50–200	25–100
Escitalopram (Lexapro)[c,d]	5	2.5 (liquid)	5	2.5	10–20	5–10
Citalopram (Celexa)[d,e]	5–10	5	5–10	5	10–40	10–30

[a]Approved by the Food and Drug Administration for depression in children and adolescents (older than 8 years).
[b]Approved by the Food and Drug Administration for obsessive-compulsive disorder in children and adolescents (older than 6 years).
[c]Approved by the Food and Drug Administration for depression in adolescents (older than 12 years).
[d]Evidence suggests QTc prolongation may be associated with higher doses of escitalopram. A Food and Drug Administration black box warning for QTc prolongation exists for citalopram doses above 40 mg in adults.
[e]Not approved by the Food and Drug Administration in children.

antidepressant trial after 8 weeks. In this treatment-resistant population, adding CBT to a medication switch was more effective (54.8% response) than a medication switch alone (40.5%) at 12 weeks of follow-up. (10)

The Food and Drug Administration (FDA)–approved selective serotonin reuptake inhibitors (SSRIs) for pediatric depression are fluoxetine (age older than 8 years) and escitalopram (age older than 12 years; Table 6). Sertraline and fluvoxamine are FDA approved in children for the treatment of obsessive-compulsive disorder. Citalopram is not FDA approved in children or adolescents but is frequently used off-label by child psychiatrists and primary care physicians. If there is no compelling reason to start use of another medication (eg, a family history of robust response to a given agent), we typically start treatment with an FDA-approved agent. It is reasonable to start treatment with fluoxetine, often at 10 mg in an adolescent and 5 mg in a preadolescent, doubling the dose after approximately 2 weeks and increasing by the initial dose every 1 to 2 weeks to the typical response range of approximately 20 to 80 mg for an adolescent to 10 to 40 mg in a preadolescent. We also often start treatment with sertraline, which due to its shorter half-life may be safer in children at high risk of adverse effects (including mania). We begin sertraline treatment at 25 mg for an adolescent and 12.5 mg for a preadolescent, increasing in a similar manner to fluoxetine to a usual range of 50 to 200 mg in an adolescent and 25 to 100 mg in a preadolescent. If there is no response by 8 weeks, adding a therapy and/or switching to a different SSRI is reasonable.

Depending on a primary care clinician's comfort level and the access to child psychiatry care, a brief consultation with a child psychiatrist may be reassuring for some primary care clinicians, especially after the first antidepressant trial. For all other primary care clinicians, a referral to a child psychiatrist is likely indicated after 2 antidepressant trials without an adequate response.

SSRIs are typically well tolerated, with the most common adverse effects being nausea, vomiting, diarrhea, constipation, headaches, sleep difficulties, and sexual adverse effects. Gastrointestinal adverse effects and headache are typically limited in duration, usually lasting less than a week, and are rarely severe enough to warrant discontinuation. We warn that these adverse effects tend to come first and benefits later, so, if manageable, the best strategy is usually to keep the dose the same rather than switching medications immediately.

There is ongoing controversy regarding SSRIs and suicidal ideation. In 2004, all antidepressants received an FDA black box warning for use in children as a result of a meta-analysis that found the average risk of suicidality in patients receiving antidepressants to be 4%, twice the placebo risk of 2%. No suicides occurred. Subsequent analyses suggested that it is approximately 11 times more likely that depressed youth taking antidepressants would benefit in terms of their depression (number needed to treat = 10) than develop suicidal ideation or attempts (number needed to treat to harm = 112). (11) Individual-level analyses of randomized clinical trials suggested no increased suicidal thoughts and behaviors in youth after starting antidepressant treatment compared with placebo and, in fact, a decrease in suicidal thoughts and behaviors in adults, mediated through a decrease in depression symptoms. Population-based studies found that, after the black box warning, rates of SSRI prescriptions decreased and the rates of suicides increased, an association that could suggest a protective effect of pharmacologic treatment. (12)

In the setting of these mixed data and the black box warning, our approach is to involve parents and adolescents in the informed consent process and use shared decision-making to carefully weigh the risks of treatment and non-treatment. We deliver a clear message that children and adolescents with depression are at risk of self-harm and must be monitored closely *regardless of treatment strategy*. Children should be monitored especially closely after starting to take antidepressant medications and after dose changes, and both parents and children should have a plan for what to do if suicidal thoughts emerge.

Another uncommon but serious adverse effect is manic activation. SSRIs can be activating in perhaps 2% to 10% of patients, although only perhaps less than 2% actually become manic. Patients with symptoms of mania and a family history of bipolar disorder may be at higher risk. (13)

Prognosis

For an untreated MDE, the median duration is approximately 1 to 2 months in community samples and 8 months in specialty clinic samples. (14) Once an MDE has reached a full remission of symptoms, we recommend continuation of therapy for a minimum of 6 months and ideally 12 months. Support for this approach includes a pediatric study that found that 6 months after an adequate response to 12 weeks of fluoxetine children continuing to take the medication had fewer relapses (42.0%) than those taking placebo (69.2%), with a longer time to relapse than the placebo group. (15)

Depression has a high rate of recurrence, reaching 20% to 60% by 1 to 2 years after remission and up to 70% after 5 years after remission. In addition, 20% to 40% of children with depression may develop bipolar disorder, especially if risk factors are present, (14) further suggesting the need for regular follow-up during the maintenance treatment phase.

BIPOLAR DISORDER AND DMDD

Controversies About Bipolar Disorder and DMDD

There have been many historical controversies around the classification of juvenile mood disorders; for much of the 20th century, it was thought that children could not experience major depression. Classically, it was also thought that bipolar disorder was uncommon in children. However, retrospective analyses with adult patients with bipolar disorder suggested symptoms began much earlier, and analyses of several longitudinal research samples suggested children had symptoms of mania.

There have been narrow, intermediate, and broad uses of the juvenile bipolar disorder diagnosis. As strictly defined by the *DSM-5* and its earlier editions, there is no special designation for pediatric bipolar disorder; the same criteria must be used for children and adults, although there is often more rapid cycling and mixed states described in children. An intermediate definition uses the same criteria for clear episodic periods of mania or hypomania but allows that these episodes can last for a shorter period of 1 to 3 days. A broader definition suggests chronic irritability as a specific childhood phenotype of bipolar disorder. (16)

As diagnoses of pediatric bipolar disorder have become more common, there has been concern in the lay literature, as well as controversy among specialists, regarding diagnostic criteria and treatment. The *DSM-5* explicitly states, "In order to address concerns about the potential for the overdiagnosis of and treatment for bipolar disorder in children, a new diagnosis, disruptive mood dysregulation disorder, referring to the presentation of children with persistent irritability and frequent episodes of extreme behavioral dyscontrol, is added to the depressive disorders for children." (1)

Despite these controversies, it is irrefutable that children who are diagnosed as having bipolar disorder and DMDD have significant morbidity at home and school, their parents have serious strains, and there are real functional and long-term developmental consequences for the child. Discussion surrounding these diagnoses will continue as the *DSM-5* is increasingly used; we hope that ongoing attention to these children will encourage further study and eventual consensus. Although the general pediatrician should not be the primary behavioral health care clinician for a child with a serious bipolar spectrum disorder or DMDD, primary care continues to play a critical role in screening, diagnosis, care coordination, documentation, and monitoring for medical complications of treatment.

Epidemiology and Pathophysiology

Given the definitional variability for childhood bipolar disorder, not surprisingly, there is heterogeneity in its reported epidemiology. For example, the National Comorbidity Survey found the combined rate of bipolar I and II disorder was 2.9%, with lifetime prevalences of 1.9% for children ages 13 to 14 years and 4.3% for children ages 17 to 18 years. (3) The 3-month prevalence of DMDD has been estimated at 3.3% in preschool samples and 0.8% in older children. (17)

As in depressive disorders, bipolar disorder has a complex origin. There is increasing evidence that genetic, perinatal, personality, and environmental factors all contribute to bipolar disorder. Neuroimaging studies have implicated brain regions in patients with pediatric bipolar disorder and in patients with DMDD phenotypes that are both shared and may differ.

Clinical Aspects

The traditional criteria for bipolar disorders are familiar to many clinicians and include periods of depression alternating with mania (bipolar I disorder) or hypomania (bipolar II disorder). Mania and hypomania are distinguished from each other by the duration of symptoms and severity of associated impairment. Core symptoms of mania and hypomania are expansive or irritable mood and abnormally increased energy or goal-directed activity, along with additional symptoms, including decreased need for sleep, grandiosity, rapid speech, and distractibility.

Children with bipolar disorder and DMDD (Table 4) typically present with mood and behavioral difficulties identified by the parents and school. Just as with depressive disorders, during the first visit, the clinician must evaluate for suicide, self-harm, aggression, substance use, and psychosis (Table 5), accompanied by a conversation about safety planning.

In addition to the classic symptoms of mania, clinicians should obtain a detailed history of representative episodes, including whether an outburst was triggered by a stressor or limit setting and the intensity, duration, and overall frequency. The clinician should also explore chronic symptoms, including baseline irritability between episodes. Symptoms may be minimized if the parents are always "walking on egg shells" to reduce the risk of outbursts. Laboratory testing or imaging is not necessary unless there are concerns for substance use or a psychotic disorder (including hallucinations or paranoia). Standardized assessments, including the Parent Version of the Young Mania Rating Scale, could be helpful.

Differential Diagnosis

The differential diagnoses for juvenile bipolar disorder and DMDD are particularly challenging, and when seriously in consideration, we encourage referral to a specialist. Normal

adolescent development can include mood swings, chronic and episodic irritability, angry arguments, irregular sleep, hypersexual thoughts, impulsive behavior, and an inflated sense of self-esteem. However, the distinguishing factor for bipolar disorder and DMDD is that symptoms are developmentally inappropriate compared with their peers, are extreme in intensity, occur in multiple settings, and cause significant functional difficulties. The differential diagnosis with MDD was noted earlier.

The primary distinction between narrow childhood bipolar disorder and DMDD is that the *DSM-5* defines bipolar disorder as an episodic illness, with clear disturbances from baseline not only of mood but also of cognitive, behavioral, and physical symptoms. In contrast, DMDD is intended to last for many months with chronic irritability. Although most children with DMDD will meet the criteria for oppositional defiant disorder, the *DSM-5* states that only 15% of individuals with oppositional defiant disorder should have DMDD because DMDD has greater severity, frequency, chronic irritability, and presence in multiple settings. Autism spectrum disorders should also be considered with severe irritability. Both childhood bipolar disorder and DMDD have significant comorbidities with ADHD, anxiety disorders, major depressive disorders, conduct disorders, and substance use disorders.

Management

Although medications are the mainstay of treatment for juvenile bipolar disorder, several psychotherapies have also been studied, including family groups, individual therapies focused on relationships and sleep, dialectical behavioral therapy, and CBT. (18) In most locations, the primary care physician is appropriately not the primary prescriber for pediatric bipolar disorder medications. However, the pediatrician should be as familiar with the basics of medications for psychiatric disorders as any other medication frequently prescribed to children.

Common mood-stabilizing medications include second-generation neuroleptics (also knows as second-generation antipsychotics), such as risperidone (with an approximate dosing range in an older adolescent of 0.5–6 mg/d), ziprasidone (40–160 mg/d), aripiprazole (2–30 mg/d), and quetiapine (200–800 mg/d; Table 7). In children there is less evidence of the efficacy of antiepileptics, such as valproate (with a goal serum level of approximately 50–100 μg/mL), lamotrigine (usually approximately 200 mg/d), and lithium (with a goal serum level of 0.8–1.2 mEq/L), although they may also be used. (19)

The primary care physician should be aware of adverse effects. The most frequent adverse effects of neuroleptics are nausea, vomiting, constipation, sedation, and headaches. In most cases, these symptoms improve over time as the body adjusts to a dose. The metabolic adverse effects of these medications are of great concern and include weight gain, hypertension, dyslipidemias, and insulin insensitivity. These adverse effects offer an opportunity for intervention by the primary care physician in terms of nutritional counseling and anticipatory guidance. Weight should be monitored monthly during medication titration, and blood pressure, fasting cholesterol levels, and fasting glucose levels should be measured every 3 months during major dose adjustments and on an annual basis thereafter.

Rare but serious adverse effects include extrapyramidal movement disorders, such as dystonias and tardive dyskinesias. Anticonvulsant adverse effects vary widely by agent but include sedation, dizziness, abdominal pain, vomiting, diarrhea, weight gain (especially with valproate), cognitive dulling, drug interactions, and, most significantly, end-organ damage or rashes that could be Stevens-Johnson syndrome. Antidepressants and stimulants are typically prescribed cautiously to children with bipolar disorder, especially in the absence of adequate mood stabilization, because both have been associated with manic activation.

Treatment studies for DMDD are ongoing. It is not yet clear if or how a DMDD diagnosis may change clinical management, although a primary motivation for the diagnosis was to reduce the prescribing of antipsychotics.

Prognosis

The controversy over nosology is driven partially by a debate about the percentage of pediatric patients diagnosed as having bipolar disorder who ultimately develop classic adult bipolar disorder. In a multisite, 4-year, longitudinal study of children diagnosed as having bipolar spectrum disorders, the predominant symptoms on follow-up were depressive or mixed symptoms and, less frequently, a clear bipolar I disorder diagnosis. (20)

DMDD was deliberately placed in the depressive disorders section because the authors thought that most of these children later had depression and anxiety, not adult bipolar disorder. For example, a previous study found that children with DMDD had greater odds of having depressive disorders in adulthood compared with children with other psychiatric disorders (Odds Ratio [OR] 4.6) or no psychiatric disorders (OR 7.4) and greater odds of having anxiety disorders compared with other (OR 3.2) or no (OR 10.4) psychiatric disorders. (21) A conflicting study suggested that DMDD is not a stable diagnosis over time and not associated with future mood or anxiety disorders. (22)

TABLE 7. **Common Medications Used for the Treatment of Bipolar Disorder in Children**

GENERIC NAME (BRAND NAME)	MEDICATION CLASS	LATE-ADOLESCENT DOSE RANGE (TOTAL DAILY DOSE) OR GOAL SERUM LEVEL
Risperidone (Risperdal)	SGA	0.5–6 mg
Ziprasidone (Geodon)	SGA	40–160 mg
Aripiprazole (Abilify)	SGA	2–30 mg
Quetiapine (Seroquel)	SGA	200–800 mg
Valproate (Depakote)	AED	Valproate level 50–100 μg/mL
Lamotrigine (Lamictal)	AED	200 mg
Lithium	Lithium	Lithium level of 0.8–1.2 mEq/L

AED=antiepileptic drug; SGA=second-generation antipsychotic.

CASE REVIEW

Jimmy presents with symptoms that meet the criteria for MDD, including irritability, insomnia (without a decreased need for sleep), anhedonia for basketball, and a decreased appetite. His symptoms do not meet criteria for DMDD because they have occurred for less than 3 months, and a 10-minute argument after limit setting is not grossly out of proportion with his age. The history should include a thorough review of suicide, self-harm, and homicidal thoughts, plans, or attempts; manic symptoms; substance use; and psychosis. There should be a thorough evaluation for comorbidities, such as anxiety and his previously diagnosed ADHD. A standardized instrument, such as the CES-D, should also be used.

If no serious symptoms arise on further history, Jimmy most likely has mild to moderate depression. To answer his mother's question, we would say, "At this time we do not believe he has bipolar disorder, but these symptoms are 'in progress' and may change over time, so we will continue to monitor closely." We would recommend a referral to an evidenced-based therapy (such as CBT), review a safety plan if symptoms were to worsen, and schedule monthly follow-ups.

If after 3 months his symptoms did not lead to a response (including as measured by a subsequent CES-D), we would recommend starting antidepressant therapy and speaking with the mother about the risks and benefits of sertraline. We would warn Jimmy and his mother that antidepressant medications can involve serial trials, given the large number of patients who do not respond to the first medication. If there were no clear benefit of sertraline after an additional 2 to 3 months, we would consider switching to fluoxetine, and if after an additional 2 to 3 months he still had an inadequate response, we would refer him to a child psychiatrist.

Summary

- On the basis of strong research evidence, depressive disorders are common in children and adolescents and are a major cause of morbidity and even mortality. (2)(3)
- The primary care pediatrician has an important role in managing depression, including through screening, diagnosis, risk assessment (especially for suicide), initiating treatment, and monitoring the illness. (7)
- On the basis of strong research evidence, cognitive behavioral therapy (8) and other psychotherapies are effective treatments for depression, and a pediatrician should refer to the appropriate specialist.
- On the basis of strong research evidence, antidepressants are also effective treatments for depression, (8)(10) especially for moderate to severe illness, or depression without a sufficient response to psychotherapy after 6 to 8 weeks. It is definitely appropriate, and often necessary, for the primary care pediatrician to prescribe first-line medications, such as selective serotonin reuptake inhibitors, including being aware of adverse effects and the black box warning about suicide.
- Some research evidence and consensus exist for the pharmacologic treatment of bipolar disorder. (19) Although the primary care physician will not likely be prescribing the medications for bipolar-related disorders and disruptive mood dysregulation disorder, the pediatrician should be aware of common and serious adverse effects and, if appropriate, be involved in monitoring weight, cholesterol levels, and blood pressure.

To view Reference list for this article, visit https://pedsinreview.aappublications.org and click on the "Mood and Affect Disorders" link.

PIR Quiz

1. You see a 16-year-old boy for evaluation of mood changes. His parents state that he has been withdrawn and isolated for at least the last 9 months. They do not identify any changes in family dynamics or structure. You tell the parents that you would like to interview the boy alone about his symptoms, privacy, and self-harm. The parents are reticent to allow you to interview their son alone, worried that your discussion will promote suicidal ideation. Which of the following responses is most appropriate?
   A. Asking about intention to self-harm does not increase risk.
   B. Refer the boy for drug testing.
   C. Refer the boy to a psychologist for further evaluation.
   D. You agree to continue the patient interview with the parents present.
   E. You will avoid any discussion of self-harm.
2. You see a 14-year-old girl who has had declining grades. She recently stopped attending basketball practice, although she was previously a star player. She sits with her family at dinner but is quiet and eats very little food. She sleeps for 11 to 12 hours per day. There is no family history of depression. Her parents ask about the next step in her evaluation and would like to make sure that all medical concerns are addressed. Which of the following studies is most appropriate for you to recommend?
   A. Comprehensive metabolic panel.
   B. Cortisol levels.
   C. Electroencephalography.
   D. Magnetic resonance imaging of the brain.
   E. Thyroid studies.
3. You see a 13-year-old girl who describes sadness and fatigue for months. You interview her privately and find she has no history or plans for self-injury. Her grandfather has a history of severe depression. Her parents would like you to help their daughter. Which of the following is the most appropriate initial recommendation?
   A. Follow-up interview in several weeks.
   B. Initiate a trial of fluvoxamine.
   C. Initiate a trial of sertraline.
   D. Inpatient psychiatric evaluation.
   E. Recommend cognitive behavioral therapy.
4. You see a 12-year-old boy who has been receiving counseling for depression with a focus on cognitive behavioral therapy. He remains isolated from family and friends and is failing academically. The counselor notes that although he has made some progress during the past month, he remains moderately depressed. She would like his treating physicians to consider prescribing medication for depression. Which of the following medications, FDA-approved for depression in adolescents, is the most appropriate recommendation?
   A. Aripiprazole.
   B. Atomoxetine.
   C. Fluoxetine.
   D. Fluvoxamine.
   E. Sertraline.
5. A 15-year-old girl diagnosed with bipolar disorder is treated with a mood stabilizing medication. Which of the following should her primary care physician monitor for adverse effects every three months during major dose adjustments?
   A. Cholesterol
   B. Complete blood count
   C. Calcium
   D. Creatinine
   E. T4

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