CME

Navigating the diagnostic challenges of bipolar disorder in youth

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ABSTRACT

Bipolar disorder in youth is difficult to diagnose and treat, but early detection is important to mitigate risks and improve patient outcomes. This article evaluates the unique challenges of diagnosing and treating bipolar disorder in children and adolescents. Bipolar disorder is associated with a significant personal and societal health burden and frequently is misdiagnosed and incorrectly treated. More research is needed to understand the pathophysiology of bipolar disorder and which treatment options are best throughout the lifespan.

Keywords: pediatric, bipolar disorder, youth, treatment, diagnostic challenges, mental health

Learning objectives

- Discuss the challenges associated with an accurate diagnosis of bipolar disorder in youth.
- Identify differential diagnoses and comorbid psychiatric conditions associated with a diagnosis of bipolar in children and youth.
- Distinguish bipolar disorder from psychiatric conditions with overlapping symptomatology.

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Bipolar disorder has a world prevalence of about 2% in children and adolescents and ranks as the fourth leading cause of disability among adolescents worldwide.[1] Bipolar disorder is associated with a host of complications, including comorbid psychiatric conditions, complicated medication regimens, and increased incidence of serious medical conditions such as cardiovascular and metabolic diseases.[2] The lifetime risk of completed suicide is up to 20 times higher in children with bipolar disorder than in the general population.[3] Suicide attempts are more common earlier in the course of bipolar, particularly during the first depressive episode, with younger age of diagnosis associated with increased risk.[4] The World Health Organization lists bipolar disorder as the second highest cause of missed worked days.[5]

Accurately diagnosing patients with bipolar disorder is key to improving outcomes and mitigating risk, but is also challenging and misdiagnosis is common. On average, patients may encounter a delay of 10 years in diagnosis and treatment; an estimated 20% of patients in a primary care setting who are diagnosed with depression may have bipolar disorder.[6]

Much scholarly debate exists about whether children with bipolar disorder present differently from adults.[7] At present, the diagnostic criteria for bipolar disorder are the same for adults and children. However, diagnosing children is challenging because their presentation may be different and they also may have more difficulty articulating their symptoms.[8] The prevalence of prepubital bipolar remains unclear, with several longitudinal studies indicating that manic and hypomanic episodes most often begin in adolescence and early adulthood.[9]

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DOI:10.1097/01.JAA.0000758200.80004.87

Key points

- Diagnostic criteria for pediatric bipolar disorder are the same as for bipolar disorder in adults.
- Up to 60% of patients with bipolar disorder present with symptoms before adulthood.
- A key diagnostic feature of bipolar disorder is a distinct change in mood and behavior from the patient's baseline.
- Reduced need for sleep accompanied by mood elevation is highly suggestive of bipolar disorder.

DIAGNOSTIC CRITERIA

The *Diagnostic and Statistical Manual of Mental Health Disorders*, 5th ed. (*DSM-5*) establishes diagnostic criteria for bipolar disorder, which it defines as a "distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently goal-directed behavior or energy."[10] Bipolar disorder is characterized as types I and II, reflecting symptomatic severity and level of impairment. The related disorders include cyclothymic disorder, substance/medication-induced, bipolar disorder due to another condition, and unspecified bipolar and related disorders. Key features of bipolar disorder are a distinct change in mood and behavior from baseline and co-occurring manic or hypomanic symptoms (**Table 1**). Hypomania is distinguished by symptoms that do not cause significant social or occupational impairment or require hospitalization and cannot include psychotic symptoms.

TABLE 1. Hypomania and mania

Per the *DSM-5*, hypomania and mania are distinct periods of abnormal and persistently elevated expansive or irritable mood, accompanied by abnormal and persistent goal-directed behavior or energy. Symptoms include inflated self-esteem, reduced need for sleep, rapid-fire speech, racing thoughts, and high-risk activities.

Hypomania

- Not severe enough to require hospitalization or cause marked impairment in the patient's social or work functions.
- No associated psychotic symptoms.
- The change is observed by others.
- The change lasts 4 consecutive days, for most of each day.

Mania

- Severe enough to cause marked impairment in the patient's social or work functions or to require hospitalization to prevent the patient from self-harm or harming others.
- The patient displays psychotic features.
- Lasts most of the day nearly every day for 1 week, or any duration, if hospitalization is necessary for mania.

Exclusion

The episode is not attributable to the direct physiologic effects of a substance or another medical condition. A full manic episode that emerges during drug or electroconvulsive therapy for depression but persists at fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and a bipolar I diagnosis.

RISK FACTORS

Bipolar disorder is associated with a high rate of global disability and a high societal burden, making early detection and intervention important goals.[5] Bipolar is one of the most heritable psychiatric disorders; monozygotic twin studies demonstrated a heritability of 40% to 70% and a prevalence 8 to 10 times higher in patients with an affected first-degree relative.[11] Numerous gene loci associated with bipolar disorder have been identified, although each appears to have a small effect, indicating the role of a wide range of polygenetic and epigenetic factors.[12]

Depression is a major component of bipolar disorder and youth typically are diagnosed with unipolar depression before being diagnosed with bipolar disorder.[13] A growing body of evidence suggests that youth at higher risk of conversion to bipolar disorder present with their first onset of depression at an earlier age and that their symptoms are more resistant to antidepressants.[13,14] Debate continues on how to account for this delay in diagnosis—whether this is the natural progression of the disorder, a diagnostic criteria shortfall, or an error in the initial assessment. However, earlier age of onset of depression does not correlate with earlier conversion to bipolar disorder, but does seem to equate with greater time between depression and later conversion.[14,15] This may suggest conversion is more associated with the natural progression of the disorder with psychosocial development. Family history is an increasingly important consideration for diagnosis and treatment decisions and should be included in the interview.

Along with genetic risks, environmental factors also are known to increase patient risk associated with the development of bipolar disorder. Adverse childhood events such as physical and emotional trauma are associated with increased risk of developing bipolar disorder.[16] Childhood trauma is thought to interact with genetic pathways that regulate neurotransmission and immunity, resulting in impairment of impulse control and emotional regulation and potentially increasing susceptibility to affective disorders.[16,17] Bipolar disorder frequently is comorbid with substance use disorders, and appears to have a bidirectional relationship; causality in either direction is difficult to prove because of the lack of quality longitudinal studies. A mounting body of evidence suggests that cannabis use increases patient susceptibility to mania and is likely an important risk factor for mania as well as other affective disorders.[18] One large prospective cohort study found that cannabis use increased the risk of first-episode bipolar disorder by a factor of five.[19] Prospective studies also indicate that opioid use is a risk factor for bipolar disorder.[20] Other drugs are likely important risk factors but remain less well studied.[18]

TABLE 2. Distinguishing symptoms of bipolar disorder

Diagnosis	Similar symptoms	Differentiating qualities
ADHD	• Distractibility • Mood fluctuations • Risk-taking • Rapid thoughts/speech • Sleep difficulties	• Patients with ADHD have difficulties with attention and focus from an early age. Often, patients have a family history of ADHD. • In patients with ADHD, mood swings, outbursts, and oppositional behavior are common with nonpreferred activities or transitions with rapid onset and resolution. • Risk-taking is typically impulsive and not out of character for patients with ADHD. • Patients with ADHD frequently talk or act out of turn. In patients with mania, rapid speech and thoughts are out of character and more tangential and difficult to follow. • Patients with ADHD often have difficulty sleeping from a young age. • Note: Symptoms of ADHD typically get better with age, compared with bipolar symptoms, which often begin in adolescence.
PTSD	• Irritability • Distractibility • Outbursts	• In patients with PTSD, irritability and distractibility are a feature of hypervigilance symptoms and often tied to triggers associated with trauma. • Outbursts in patients with PTSD often are associated with trauma history and accompanied by hyperarousal and avoidance symptoms.
GAD	• Anxiety • Sleep disturbances • Restlessness • Distractibility • Irritability	• Anxiety is characterized by excessive worries (social, work, school, environment). Thought process is usually less tangential than mania. • In patients with GAD, poor sleep quality is distressing and contributes to fatigue and irritability. • Patients are preoccupied with anxiety triggers. GAD symptoms are typically more amenable to counseling and suggestion. • Fatigue is common in patients with GAD.
Borderline personality disorder	• Impulsivity • Risk-taking behaviors • Mood instability • Angry outbursts	• In patients with borderline personality disorder, impulsivity is related to interpersonal relationships. • Risk-taking behavior is characteristic of the patient. • Changes of mood and affect are rapid. Tendency for unstable and intense interpersonal relationships. • Persistent pattern of outbursts, often sudden and out of proportion to a given situation. Abandonment is a common theme. Recurrent suicidal threats/gestures. • Note: Diagnosis of borderline personality disorder is controversial in youth, but may be valid and reliable in mid- to late-adolescence.
Major depressive disorder (MDD)	• Irritability/anger • Sleep disturbances • Distractible	• MDD is also accompanied by feelings of sadness, worthlessness, and anhedonia. • Reduced need for sleep is suggestive of bipolar disorder. • Difficulty making decisions is more characteristic of MDD; racing thoughts are more common with mania. • Note: Important to screen for mania symptoms when evaluating for depression. Collateral can be particularly helpful.
DMDD	• Outbursts • Mood—irritable/angry	• In patients with DMDD, mood is persistently irritable or angry most of the day, nearly every day, and is observed by others. In patients with bipolar disorder, the mood and behavioral disturbance should be a distinct change from baseline.

DIAGNOSTIC CHALLENGES

The presentation of a patient with bipolar disorder can vary greatly based on what part of the cycle the patient is in and the severity of the disorder. A careful history is paramount to distinguish various psychiatric diagnoses with overlapping symptoms (**Table 2**). Clinicians may use a screening tool to aid in assessing for bipolar disorder along with other screening tools for depression and anxiety. The Mood Disorder Questionnaire (MDQ) is one of the most common tools used to screen for bipolar disorder.[21] Although this tool is helpful, it should be used as an aid in building the patient's history and not as a qualitative diagnostic test. For instance, some patients may check positive on the list, but more in depth questioning may reveal misinterpretation of the questions, subthreshold symptoms, and frequently, symptomatic asynchrony with mood disturbance.[22] For children and youth, two assessment scales are commonly used—the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) mania rating scale and the Young Mania Rating Scale (YMRS). Both of these scales are lengthy and typically reserved for research settings, and a recent multivariant metanalysis has called into question the validity of the YMRS.[23] Other clinical scales that assess for manic symptoms and have been validated include the MDQ, the General Behavior Inventory (GBI), and the Child Mania Rating Scale (CMRS). The GBI and CMRS have been slightly modified and verified for use by parents to help monitor and measure

changes in symptoms of bipolar disorder in children and youth over time.[24,25] These scales are useful, but direct patient interview and collateral information from caregivers and teachers is needed to enhance diagnostic validity.

Periods of reduced need for sleep are an important characteristic of bipolar disorder, but must be distinguished from other disorders related to sleep disturbances. For example, difficulty falling asleep is common in patients with depression, generalized anxiety disorder (GAD), or attention deficit hyperactivity disorder (ADHD), but results in fatigue and irritability the next day.[26] The key for bipolar disorder is a reduced *need* for sleep—although patients sleep fewer hours, they do not report increased daytime fatigue or somnolence. Reduced need for sleep with co-occurring mood elevation is highly specific for pediatric bipolar disorder.[27] Sleep deprivation, such as may occur after a child is born, may induce a manic episode in a patient with bipolar disorder.

Frequently, parents and patients complain of "mood swings," but this warrants further exploration because this is nonspecific and often different than the episodic mood shifts characteristic of bipolar disorder. These "mood swings" more often represent a patient with rapid changes in acute mood and affect, such as a child who is easily angered or upset, which is common in post-traumatic stress disorder (PTSD), depression, anxiety, ADHD, and children of overly permissive parents. Likewise, hypervigilance symptoms of PTSD can be described by caregivers as mood swings. A more accurate clinical description of the patient with bipolar disorder is *intermittent mania or hypomania* rather than a history of *mood swings*, which can be confusing to both patient and clinician. The key for the clinician is to distinguish a true manic episode from nonspecific fluctuations in mood associated with many psychiatric conditions, situational stressors, and normal development. This necessitates a more precise discussion of manic/hypomanic episodes with patients and caregivers. Similarly, when gathering family history, clarify symptoms when possible, because a psychiatric diagnosis can be misunderstood and misrepresented (for example, depression or substance use disorder). Symptoms of hypomania are more subtle and may be missed or ignored by parents and patients who benefit from the positive effects.

Irritability is a much more common symptom than elevated mood, but again, this symptom is nonspecific and merits further characterization.[28] Irritability and distractibility also are part of the symptomatology of bipolar disorder but must be distinguished from normal childhood and adolescent behaviors. These symptoms are frequent complaints of patients with depression, anxiety, ADHD, PTSD, or unstable homes in general. The distinguishing feature in bipolar disorder is the distinct change in baseline behavior and mood. Some youth present with severe and persistent irritability and/or anger and lack a history of episodic change from baseline, and in these patients, a diagnosis of disruptive mood dysregulation disorder (DMDD) may better describe their clinical picture.[8,29]

As with adults, consider substance use disorders to explain a sudden change in baseline behavior and mood. When appropriate, periodic drug screening can be a useful tool to help exclude a substance use disorder. Co-occurring substance use disorder is not uncommon in patients with bipolar disorder and may induce an early manic episode in youth.[30]

DIFFERENTIAL DIAGNOSIS

Clinicians face several challenges when trying to distinguish bipolar disorder from other psychiatric conditions that share symptoms and have high rates of comorbidity. The differential diagnosis includes DMDD, PTSD, ADHD, substance use disorders, depression, GAD, oppositional defiant disorder (ODD), and schizophrenia. A recent meta-analysis showed the four most common comorbid psychiatric conditions were anxiety disorders (54%), ADHD (48%), disruptive behavior disorders (31%), and substance use disorders (31%).[30] Medical conditions to rule out include thyroid and adrenal disorders, anemia, brain lesion, head trauma, and when possible, intrauterine drug exposure.[31] Potential for medication-induced mania or hypomania symptoms is associated with corticosteroids, stimulants, and antidepressants.[32] Induction of manic symptoms by these medications should raise the index of suspicion, but is not itself necessarily diagnostic of bipolar disorder. The exception as detailed in the *DSM-5* is a patient with full manic symptoms that emerge during antidepressant treatment and who remains fully syndromal beyond the expected physiologic response time expected from the treatment.[10]

ADHD

ADHD is one of the most common childhood psychiatric conditions, with an estimated global prevalence of 5% to 12%.[33] ADHD and bipolar disorder have many overlapping symptoms, including distractibility, mood fluctuations, risk-taking, sleep difficulties, and rapid thoughts and speech.[10,34] The history of onset and symptom progression is a key element, because symptoms of ADHD present early and typically improve with age; manic symptoms rarely begin before adolescence, with a peak prevalence of age 21 to 25 years.[35] Assessing for a family history of mental illness is important because ADHD and bipolar disorder both have high heritability. In patients with ADHD, emotional outbursts and irritability often can be tied to nonpreferred activities and transitions and frequently are accompanied by predictable oppositional behaviors. In a child with ADHD, these outbursts can be dramatic, but the onset and resolution typically are of short duration. To meet the *DSM-5* criteria for hypomanic symptoms, the irritability should be present for most of the day and last at least 4 consecutive days.[10] Rapid speech and hyperactivity are hallmarks of ADHD and are accompanied by a

tendency to talk and act out of turn.[10] During a manic episode, speech becomes fast and often accompanied by animated gestures and expansive affect that is uncharacteristic of the patient. The logic of the patient's dialogue may be difficult to follow, with a thought pattern that is rapid and tangential.

Risk-taking behaviors are common in patients with ADHD, resulting in higher rates of injury and punitive actions at home, school, and within the justice system.[36] In youth with ADHD, these risk-taking behaviors and actions are typical to the child who has a long history of accidentally getting in trouble. A youth with bipolar disorder also may partake in high-risk activities, but these incidents are distinguished from ADHD by being outside of the youth's usual behavior and co-occurring with other manic or hypomanic symptoms. These high-risk activities often play into the paradigm of goal-directed activity associated with a manic episode—for example, excessive interest in a project, intense desire to travel, and sudden intense romantic relationships. The risky actions may seem nonsensical and frequently are better characterized as compulsive rather than impulsive.

Sleeping challenges often are reported by parents of youth with ADHD because these patients have a harder time falling asleep, though they may need a little less sleep than a youth who does not have ADHD.[37] Without enough sleep, the youth with ADHD often demonstrates increased symptomatology, especially increased irritability and hyperactivity. In contrast, a youth with a manic or hypomanic sleep pattern may only sleep 3 to 4 hours a night for consecutive nights, yet still feels rested.[10]

PTSD

PTSD shares symptoms of irritability, distractibility, and sleep disturbances with bipolar disorder. For a diagnosis of PTSD, the patient must have experienced or witnessed a traumatic event such as death, serious injury, or sexual violence.[10] Though a patient's obvious trauma history can help clinicians diagnose PTSD, it makes a diagnosis of bipolar disorder more difficult. A traumatic history can be difficult to elucidate from a patient who may be reluctant to disclose such details for fear of stigma, social reprisals, or as an act of avoidance.[10] Clinicians must keep PTSD in the differential diagnosis as they build rapport with the patient, and must be vigilant for symptoms indicative of PTSD, such as hyperarousal, avoidance, disassociations, self-destructive behaviors, and nightmares. With PTSD, irritability and angry outbursts can occur with little provocation and commonly are associated with trauma-related triggers.[10] Patients and other informants may describe these outbursts and irritability as *mood swings* and may even label the events as *bipolar* in a colloquial sense to describe rapid changes of mood that are difficult to explain and interpret. A patient with comorbid PTSD and ADHD can present with a cluster of symptoms that appear strikingly similar to bipolar disorder; these symptoms may be especially common in children under the care of Child Protective Services or in group homes.[38] Children in foster care represent a vulnerable group with diverse needs and have been found to be three times more likely to be prescribed psychotropic medications than other children.[39] As rapport is developed, clinicians should be mindful of patterns of distress associated with certain people, places, or subjects that warrant further exploration of trauma history. Also, note that previous research has indicated that treatment-resistant PTSD is a predictor of comorbid bipolar disorder.[40]

GENERALIZED ANXIETY DISORDER

Anxiety is among the most common pediatric psychiatric conditions, with the onset of GAD common during puberty.[41] Patients with GAD often exhibit symptoms of restlessness, sleep disturbances, distractibility, and irritability.[10] Anxiety is characterized by excessive worries and perseveration that can be akin to the excessive goal-directed activity of a patient with bipolar disorder during a manic episode. With GAD, the preoccupations are more heterogeneous, such as concern for good grades, social interactions, and anticipated changes. The patient with GAD is not only preoccupied with potential stressors but also worries about anxiety itself and the impairments that may result when faced with a stressor. Excessive worry in a patient with GAD often results in disturbed sleep, but unlike the reduced sleep typical of a patient during a manic or hypomanic episode, the lack of sleep is distressing to the patient and contributes to fatigue and irritability. Patients with GAD are likely to feel exhausted by the relentless struggle to cope with their symptoms, and comorbid depression is common.[42] These patients often respond to psychotherapy and a selective serotonin reuptake inhibitor.[43,44]

BORDERLINE PERSONALITY DISORDER

Personality disorders are among the most controversial subjects in the study of psychopathology, especially when considering how they may apply to children. A growing body of evidence over the past 2 decades indicates the validity and reliability of the diagnosis of borderline personality disorder in mid to late adolescence when traits are exhibited for at least a year.[45] Borderline personality disorder is characterized by a persistent pattern of difficult interpersonal relationships, impulsivity, unstable sense of self, and affective instability.[10] The symptomatology of borderline personality disorder can lead the patient and others to describe *mood swings* or use the term *bipolar* in a colloquial fashion to mislabel these rapid changes in mood. These mood fluctuations often are intense and disproportionate to a given situation, but typically of short duration, rarely lasting more than a day.[10] Impulsivity takes many forms, including high-risk behaviors (substance use, risky or self-endangering sexual behaviors, reckless behavior) and may include recurring self-harm or suicidal

gestures.[10] Inattention and hyperactivity are common, and childhood diagnosis of ADHD/ADD is common and has predictive value for later diagnosis of borderline personality disorder.[46] Concerns of abandonment is a common theme in patients with borderline personality disorder and may result in impulsive and manipulative behaviors.[10] Though a patient with borderline personality disorder is impaired by intense emotional instability and interpersonal strife, the pattern is distinguished from mania or hypomania because the borderline traits are persistent and enduring and do not represent a distinct change from their baseline.[10]

DIAGNOSTIC CONTROVERSIES

The controversy surrounding pediatric bipolar disorder has been focused on questions of diagnostic criteria and concerns about the increased use of second-generation antipsychotics in these patients.[10,47] In the 1990s, some experts advocated a different diagnostic criterion, postulating that persistent irritability represents a unique characteristic of pediatric bipolar disorder.[27] There is now broad, though not universal, consensus that the same criteria for diagnosing bipolar disorder should be used in children and adults.[48] Longitudinal studies suggest that children with persistent irritability are not more likely to convert to bipolar disorder as they mature.[49] Children with severe persistent irritability are now likely to be diagnosed with DMDD and are at a higher risk of unipolar depression later in life.[50]

A significant minority of patients do not fit into the current diagnostic classification system.[51] The *DSM-5* tried to address this issue with modifiers such as *mixed features*, but this may have only added to the confusion.[52] Many of these patient subtypes are placed into the category of cyclothymia because they present with subthreshold symptoms of mania and depression or unspecified bipolar when manic or hypomanic symptoms do not meet the specified time criteria in the *DSM-5*.[53] Questions remain about how to best characterize and classify patients with mixed states, such as depressive episode with mixed features, with anxious distress, or mania/hypomania with mixed features.[54]

No imaging, neurologic screening, or blood test can aid in the diagnosis of bipolar disorder. Early detection is a major goal, but this requires a better understanding of risk assessment. How should clinicians manage high-risk youth (such as those who have subthreshold presentation with a strong family history of bipolar) and how can their treatment be optimized? Should mood stabilizers be started early in high-risk patients? Should antidepressants be avoided in patients who are considered high-risk, but do not meet criteria for bipolar or its subtypes? Further longitudinal studies are needed to help address questions of risk assessment and mitigation. Environmental influences such as trauma and substance use are important risk factors but questions remain about how to best address these.

CONCLUSION

Bipolar disorder often is challenging to diagnose and complicated to manage, requiring continuing evaluation and medication assessment. More research is needed to understand the pathophysiology of bipolar disorder and which treatments are best throughout a patient's lifespan.

Identifying bipolar disorder early and initiating appropriate treatment and monitoring can mitigate the risk of substance use, suicide, and other undesirable outcomes for patients. Clinicians must be equally cautious to avoid a misdiagnosis that would expose youth to unnecessary medications and treatments. **JAAPA**

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