The Clinical and Treatment Implications of Co-Occurring Mania and ADHD in Youths

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By Janet Wozniak, MD [5]

The relationship between bipolar disorder and ADHD remains unclear; however, this combined condition may represent an important genetic and clinical subtype with distinct psychopathology, familiality, and treatment response.

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Educational Objectives

After reading this article, readers should be able to:
• Better appreciate the familial role in ADHD
• Recognize the implications of ADHD and bipolar comorbidity
• Understand the overlapping psychopathology and diagnostic issues associated with ADHD and bipolar comorbidity
• Comprehend the psychopharmacological response in comorbid ADHD and bipolar disorder
• Initiate a treatment strategy that may include mood stabilizers and stimulant medications

Who will benefit from reading this article?
Psychiatrists, child and adolescent psychiatrists, psychologists, primary care physicians, nurse practitioners, and other health care professionals.

Is bipolar disorder overdiagnosed in youths? Public and scientific debates have focused on the controversial topic of whether some children with emotional and behavioral problems are receiving an incorrect diagnosis of bipolar disorder and are being exposed unnecessarily to the adverse effects of mood stabilizing medications. On the other hand, it may be that because of skepticism and diagnostic confusion, bipolar disorder has been, and continues to be, underdiagnosed in youths, with many children left untreated despite FDA approval of potentially useful medications for children as young as 10 years. Thus, efforts to better understand the issues of diagnostic confusion are of extremely high clinical, scientific, and public health importance.

A major component of the debate regarding the validity of the diagnosis of bipolar disorder in youths rests with its high overlap with ADHD. Distractibility, physical hyperactivity, and talkativeness are symptoms of both ADHD and mania. Arguably, all the symptoms of ADHD, including inattention, impatience, disorganization, and restlessness, could be part of the mania component of bipolar disorder.

By the same token, many of the symptoms of mania, such as euphoria (giddy, silly) or irritability (low frustration tolerance), reckless impulsivity, and racing thoughts, could be construed to occur at least some of the time as part of ADHD. ADHD also can include a component of emotional dysregulation, which further complicates the diagnosis.

Epidemiology of ADHD and bipolar disorder
While not all training programs include education in pediatric bipolar disorder, all child and adolescent psychiatry residents and most pediatricians are well acquainted with the diagnosis of ADHD, which is one of the most common reasons for psychiatric treatment in pediatric patients. ADHD is a highly morbid, well-characterized, and valid disorder with onset in childhood; it affects more than 5% of youths.

While bipolar disorder in adults has long been considered to be one of the most disabling conditions seen in psychiatric practice, the condition in children has only recently been the focus of research to establish its validity. Because of a lack of accurate epidemiological reports, researchers had
estimated, based on indirect evidence, that bipolar disorder affects approximately 1% of children and adolescents. However, a recent epidemiological study of more than 10,000 US adolescents reports a rate of 2.9% (2.6% are severely impaired). A recent meta-analysis performed by Van Meter and colleagues of international epidemiological studies of pediatric bipolar disorder from 1985 through 2007 showed an overall prevalence of 1.8%. The researchers noted that there was no significant difference in the rates between US and non-US studies, and there was no evidence of an increase in the community over time.

**Distinguishing symptoms**

While mania can present as either euphoria or extreme irritability, findings suggest that irritability may be the more common manic mood symptom in youths. While a case can be made that the irritability of mania is distinctly and qualitatively different from other forms of irritability, when present in a child with ADHD, irritability or angry outbursts may be misattributed to the frustration of living with ADHD and attendant impulsivity rather than to co-occurring mania. Conversely, inattention, distractibility, and talkative-ness in a child or adolescent with bipolar disorder may erroneously be attributed to residual mania rather than ADHD.

According to diagnostic criteria, episodicity is a definitional feature of bipolar disorder and can be a useful marker of mania, just as chronicity or cross-situationality is a diagnostic feature of ADHD. However, the documented chronicity and complex/rapid cycling of bipolar disorder in youths often renders the notion of classic episodicity as a distinguishing feature of mania functionally impracticable. While many adults with bipolar disorder present with chronicity, mixed states, and irritability as the clinical picture, this presentation has been the subject of debate when it occurs in children. Whether this presentation is valid for bipolar disorder for some patients remains a scientific and clinical question.

In clinical practice, the question of whether mood-dysregulated, hyperactive, and inattentive youths have bipolar disorder, ADHD, or both has critical clinical and therapeutic implications. Medications for ADHD may worsen mania, and medications for mania are fraught with adverse effects and may not be effective for the treatment of ADHD. Because ADHD and mania exhibit similar symptoms, there is a risk of unintentional overdiagnosis or underdiagnosis of one or the other. Milberger and colleagues demonstrated that most of the children in their study with the combined disorders continued to meet criteria for both mania and ADHD after overlapping symptoms were discounted. This suggests that bipolar disorder and ADHD comorbidity is not a methodological artifact that results from shared diagnostic criteria.

The co-occurrence of bipolar disorder and ADHD has long been an “orphan” condition, neglected in adults because of past skepticism regarding the continuity of ADHD into adulthood and neglected in children because of the now debunked concept that bipolar disorder does not occur in the young.

**The case for a unique subtype**

A bidirectional overlap is well documented between ADHD and bipolar disorder. Among children with bipolar disorder, rates of co-occurring ADHD range from 57% to 98%, with higher, almost universal rates among prepubertal children. ADHD has also been reported in samples of adults with bipolar disorder. In a longitudinal study of boys with ADHD, 17% were found to have co-occurring bipolar disorder at baseline. Other studies of ADHD, such as the Multimodal Treatment of ADHD (MTA) study, found rates of any mood disorder, depression or bipolar, to be too low for hypothesis testing, possibly an outcome related to exclusionary criteria for bipolar disorder (as well as psychosis, suicidality, and homocidality).

Faraone and colleagues found higher rates of ADHD in persons with childhood-onset bipolar disorder than in persons with adolescent-onset bipolar disorder. Those findings were consistent with a report from West and colleagues that 57% of adolescents with bipolar disorder also had ADHD. The prevalence reported in preadolescent samples is much higher and ranges from 70% to 98%. These results suggest that co-occurrence with ADHD is a marker of preadolescent-onset mania. This form of very early-onset mania may represent a developmental subtype of the disorder.

The clinical features of mania in children with comorbid ADHD and bipolar disorder provide further evidence that this subtype represents a developmentally distinct variant. Mania in these children is more often characterized by violent irritability and prolonged and aggressive temper outbursts, rather than euphoric mood. The type of irritability observed in manic children is very severe, persistent, and often violent. It is distinctly different in quality and severity from other forms of irritability, such as the low frustration tolerance of ADHD or the “mad, cranky” irritability of childhood depression.

The natural course of bipolar disorder in pediatric cases tends to be chronic, complex/rapid cycling, and continuous (and mixed with depression) rather than episodic and acute. This is due in part to
the complex and continuous cycling of mania and depression (with switches in polarity and the melancholy and lower level irritability of depression and the euphoria and extreme irritability of mania) as well as the interplay of bipolar disorder with its comorbid conditions, notably ADHD. Thus, children with comorbid bipolar disorder and ADHD are rarely “well.”

In a review of 10 years of research on pediatric mania, Geller and Luby\(^\text{18}\) concluded that childhood-onset mania is a nonepisodic, chronic, rapid cycling, mixed manic state. Similar findings also suggest that in the overwhelming majority of bipolar children, the disorder is chronic (they are seldom well) and the presentation is mixed.\(^\text{15}\) A follow-up study showed that the youths (N = 78) continued to experience persistent disorder, including depression and subthreshold states of mania. Only 6.4% were euthymic without treatment at 4 years.\(^\text{21}\)

The Course and Outcome of Bipolar Illness in Youth (COBY) study demonstrated an episodic course with spontaneous improvements and deteriorations in mood and energy. On average, patients were ill for 60% of the follow-up time. Most patients (81.4%) recovered from their index episode, but time to recovery was a median of nearly 2.5 years. Of those who recovered, 62.5% had a full syndromal recurrence a median of 1.4 years following symptom remission.\(^\text{22}\)

Because of overlapping features, comorbid bipolar disorder and ADHD is difficult to diagnose. In addition to the full symptom profiles of both mania and ADHD, the comorbid condition has correlates of both disorders.\(^\text{15}\) Children who meet the criteria for ADHD show high rates of conduct and oppositional defiant disorders and of learning disorders and need for academic support. Depression and psychosis as well as poor functioning—all common correlates of bipolar disorder—are also usually present.\(^\text{23}\)

While ADHD and mania have been found to co-occur in pediatric populations, the National Comorbidity Survey Replication epidemiological study also has documented high bidirectional comorbidity between bipolar disorder and ADHD in adults. Study results showed significantly higher rates of bipolar disorder in adults with ADHD than in those without bipolar disorder (19.4% vs 3.1%). Equally high rates of ADHD were seen in adults with bipolar disorder compared with those without bipolar disorder (21.2% vs 3.5%).\(^\text{24}\)

**The familial connection**

Although the mechanisms that mediate the association between bipolar disorder and ADHD are not entirely clear, ADHD and bipolar disorder individually and together are known to have strong familial links. Children of bipolar parents have an elevated risk of ADHD, and relatives of children with ADHD are at increased risk for bipolar disorder.\(^\text{25,26}\) However, the combined condition appears to be common in these families. In children of bipolar parents, the risk of ADHD is higher in children with bipolar disorder.\(^\text{27}\)

Consistent with the notion of a subtype, relatives of patients who have comorbid bipolar disorder and ADHD are at increased risk for the combined condition.\(^\text{19,20}\) This suggests that the disorders are transmitted together and not independently. Faraone and colleagues\(^\text{25,28}\) studied the familial transmission of these disorders in children with ADHD. The pattern of transmission seen in the studies supported the hypothesis that the comorbid condition could represent a distinct condition. Studies of adults with bipolar disorder suggest that comorbid ADHD may be a marker for an early-onset subtype. Winokur and colleagues\(^\text{29}\) found that bipolar adults were more likely to have shown traits of hyperactivity in childhood. Sachs and colleagues\(^\text{30}\) reported that among adults with bipolar disorder, a history of comorbid ADHD was only evident in those with onset of bipolar disorder before 19 years of age. The mean onset of bipolar disorder in those with a history of childhood ADHD was 12.1 years.

Nierenberg and colleagues\(^\text{11}\) reported that adults with comorbid bipolar disorder and ADHD had distinct features of bipolar disorder, including early onset, shorter periods of wellness (chronicity), greater comorbidity, and a worse course overall. These features are frequently characteristic of the bipolar disorder seen in children.

Consistent with the documented association of comorbid ADHD almost exclusively with early-onset bipolar disorder, a relatively low lifetime prevalence (9.5%) of comorbid ADHD has been reported in adults with bipolar disorder with heterogeneous age at onset.\(^\text{11}\) Perlis and colleagues\(^\text{31}\) found that 65% of adults with bipolar disorder in a large sample (N = 1000) had early onset of the disorder (younger than 18 years). In the adults who had early onset, there were greater rates of comorbid anxiety disorders and substance abuse, more recurrences, shorter periods of euthymia, and a greater likelihood of suicide attempts and violence. The rate of ADHD was 20.7% among the earliest-onset group (younger than 13 years), 7.6% in the intermediate-onset group (13 to 18 years), and 5.7% in those with onset after 18 years. The age at bipolar onset appears to modify the risk of comorbid ADHD. The researchers concluded that age of onset may cleave a distinct form of bipolar disorder.
disorder, which is more likely to be comorbid with ADHD. The study by Chang and colleagues of children of parents with bipolar disorder supports this notion. The findings suggest that bipolar disorder in high-risk children is associated with early-onset bipolar disorder in the parent and a parental history of ADHD. The age at onset of mania in adults with bipolar disorder and a history of ADHD was 11.3 years. The study by Geller and coworkers showed similar results—bipolar disorder comorbid with ADHD was a proxy for early onset. Further highlighting the importance of age at onset are the findings of Lin and colleagues. The results of their study showed that relatives of patients with early-onset bipolar disorder were more likely to also have early-onset bipolar disorder. The pattern of transmission seen in families suggests that early-onset mania, which is largely associated with ADHD, might be a familial distinct subtype of bipolar disorder.

Faraone and colleagues used familial risk analysis to examine the association between ADHD and mania. They found that relatives of children with comorbid ADHD and bipolar disorder were at high risk for ADHD that was indistinguishable from the risk in relatives of children with ADHD and no bipolar disorder. However, comorbid bipolar disorder and ADHD and bi-polar disorder alone selectively aggregated among relatives of youths with bipolar disorder compared with those with ADHD but without bipolar disorder. Almost identical findings were obtained in the family study by Wozniak and colleagues. Bipolar parents of children with comorbid ADHD and bipolar disorder had a childhood history of ADHD, a mixed manic presentation, and juvenile-onset bipolar disorder.

**Psychopharmacology**

Emerging neurobiological correlates are the focus of recent research, and a wide array of FDA-approved treatments is available for ADHD. While the recognition and treatment of ADHD in adults has lagged, research documenting the continuity of ADHD into adulthood has established ADHD as a disorder with lifelong implications. Pediatric bipolar disorder, a long-neglected diagnosis, is gaining acceptance in the clinical and research community as a valid clinical entity. The FDA has approved 5 medications (risperidone, aripiprazole, quetiapine, olanzapine, and lithium) for treatment of bipolar disorder in youths—with some medications approved for children as young as 10 years. Findings from clinical practice indicate that the use of atypical antipsychotics for the treatment of mania and mixed states is common in pediatric patients. Although empirical evidence for the psychopharmacological response in comorbid bipolar disorder and ADHD is limited, many youths with bipolar disorder also receive treatment for comorbid ADHD. In a recent chart review of psychopharmacological interventions in clinically referred youths with bipolar disorder, 60% were treated for ADHD with stimulants and atomoxetine. ADHD symptom improvement was seen in 56% of the patients. Stimulant medications may increase the risk of exacerbating mania; thus, clinical good sense dictates that the treatment of ADHD be addressed only after the symptoms of bipolar disorder are stabilized. In mood-stabilized youths who have bipolar disorder, ADHD symptoms often become the second most severe presenting complaint. The decision to treat comorbid ADHD following stabilization of mania should be guided by clinically determining the level of impairment associated with ADHD.

Lamotrigine and divalproex are FDA-approved for use in bipolar adults, but they do not have a psychiatric indication for youths. However, emerging research suggests that lamotrigine may be useful in youths with bipolar disorder. Carbamazepine (used off-label) has been evaluated, with positive results. Divalproex, on the other hand, has not shown therapeutic efficacy in youths with bipolar disorder. The efficacy of antimanic medication for bipolar disorder has been confirmed in more than 2500 pediatric patients. Antimanic and mood stabilizing agents on their own may have anti-ADHD effects. Carbamazepine and risperidone improve ADHD symptoms in youths with bipolar disorder, although this improvement may be attributable to the overlapping symptoms of ADHD and mania. In a recent controlled trial of youths with bipolar disorder, aripiprazole was not found to be superior to placebo in improving ADHD symptoms. The response to lithium and divalproex is greater in youths with comorbid bipolar disorder and ADHD than in those without comorbid ADHD. The subtype of comorbid bipolar disorder and ADHD may have unique treatment requirements.

While concern exists regarding the mood destabilizing effects of stimulant medication in bipolar disorder, a controlled trial found adjunctive mixed amphetamine salts to be safe and efficacious for the treatment of ADHD in patients with bipolar disorder whose symptoms have been stabilized with divalproex. Findling and colleagues reported that concomitant treatment with methylphenidate

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(MPH) improved symptoms of ADHD without destabilization of mood in youths with bipolar disorder. MPH adjunctive therapy for ADHD in bipolar youths who have been stabilized with aripiprazole was not superior to placebo, and in 1 patient who received MPH and aripiprazole, severe mood destabilization developed.51 Chang and colleagues52 reported that atomoxetine added to antimanic agents was well tolerated and efficacious in the treatment of ADHD in a small sample (N = 12) of youths with comorbid bipolar disorder. ADHD symptoms in adults with comorbid bipolar disorder and ADHD improved with bupropion treatment, without activation of mania.53 These aggregate data suggest that ADHD can be safely and effectively treated in patients with stabilized bipolar disorder, although caution is always indicated.

**Conclusion**

The relationship between bipolar disorder and ADHD remains unclear; however, this combined condition may represent an important genetic and clinical subtype with distinct psychopathology, familiality, and treatment response. Further research to examine the distinct nature of comorbid bipolar disorder and ADHD is needed.

Using DSM-IV criteria, comorbid bipolar disorder and ADHD has been identified in pediatric and adult samples, despite overlapping symptoms. Clinical trials point to the safety and efficacy of using combined pharmacotherapy to address both disorders. Heterogeneity in bipolar disorder is well accepted; stratifying by comorbidity with ADHD may mark an early-onset subtype of bipolar disorder worthy of independent study.

**References:**

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