

Bipolar Disorder and Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

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The relationship between bipolar disorder and attention-deficit/hyperactivity disorder (ADHD) in children and adolescents has been one of the most hotly debated topics in recent child psychiatry literature. At the heart of the matter is whether large numbers of children with bipolar disorder are being unrecognized or misdiagnosed. The differential diagnoses of juvenile-onset bipolar disorder can be complicated by many factors, but the most common clinical dilemmas seem to arise from overlapping symptomatology with ADHD and the differing treatment strategies these diagnoses imply. This article discusses the similarities and differences between these disorders with respect to phenomenology, epidemiology, family history, brain imaging, and treatment response.

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Whether large numbers of children with bipolar disorder are being misdiagnosed with attention-deficit/hyperactivity disorder (ADHD) is a topic that has generated considerable controversy in recent child psychiatry literature. A series of studies¹ from Harvard indicate that the rate of bipolar disorder in juveniles may be much higher than previously reported. On the basis of questionnaires administered in their ADHD clinic, 22% of subjects met criteria for bipolar disorder, 30% if subjects had ADHD comorbid with oppositional defiant disorder.¹

Other investigators, including ours at the Child Psychiatry Branch of the National Institute of Mental Health, do not find large numbers of bipolar disorder subjects in their ADHD samples, possibly reflecting differences between clinical and research samples.

If large numbers of juveniles with bipolar disorder are being misdiagnosed as having ADHD, or if significant comorbidity with bipolar disorder is being overlooked, this issue would be of paramount importance to children and the field of child psychiatry.

To examine the relationship between bipolar disorder and ADHD and to help discern the critical clinical distinction between them, the disorders will be discussed with respect to phenomenology, epidemiology, genetics, brain imaging, and treatment response.

PHENOMENOLOGY

DSM-IV diagnostic criteria² for bipolar disorder and ADHD directly overlap for symptoms of talkativeness, distractibility, and psychomotor agitation. Other criteria, although not directly overlapping, can be difficult to discern clinically, for example, "decreased need for sleep" in bipolar disorder versus sleep difficulties common in ADHD, "flight of ideas" in bipolar disorder versus "difficulty sustaining attention" in ADHD, and "excessive involvement in pleasurable activities that have a high potential for painful consequences" in bipolar disorder versus "impulsivity" in ADHD. Other features of the disorders that overlap are impairments in social and family relationships, school performance, and self-esteem.

However, despite the considerable overlap, a few criteria yield quite good discriminating power for the two disorders. In the largest well-controlled study to date, Geller and colleagues³ examined 60 children with bipolar disorder and 60 with ADHD and reported that elevated mood occurred in 87% of children with bipolar disorder, but only in 5% of children with ADHD; grandiosity occurred in 85% of children with bipolar disorder versus 7% of those with ADHD. Decreased need for sleep, racing thoughts, and hypersexuality were also noted to be much more common in bipolar disorder than in ADHD.³

The clinical distinctions are complicated by the fact that both bipolar disorder and ADHD are highly comorbid with other disorders, such as oppositional defiant disorder or conduct disorder. Also, ADHD is common in juveniles with bipolar disorder,⁴⁻¹⁰ although longitudinal studies of ADHD have generally not shown an increased incidence of bipolar disorder.¹¹

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The diagnosis of both disorders relies heavily on life-long history, and the use of life charts to map the course of symptomatology throughout development is particularly helpful for diagnosis. Since the acute phase of bipolar disorder may present a very confusing clinical picture, the lifetime history can often provide important differentiating points.

Although DSM-IV has no separate criteria for juvenile-onset bipolar disorder, many clinicians and researchers feel that the phenomenology is significantly different between children and adults. A key distinction is the lack of discrete episodes of mania. In a review of the literature of child and adolescent bipolar disorder from 1987 to 1997, Geller and Luby¹² conclude that juvenile-onset bipolar disorder is characterized by nonepisodic, chronic, rapid-cycling, mixed manic states. Experienced clinicians also note that adults with bipolar disorder who report childhood onset almost always describe a chronic mixed state (R. M. Post, M.D., oral communication, Jan. 2000). In this sense, the disorder may fit more closely with DSM-IV criteria for cyclothymic disorder.

Others, however, argue that "discrete episodes" are the sine qua non of bipolar disorder.¹³ Indeed, the criteria in DSM-IV define a manic episode as a "*a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)* [italics added]."^{22(p332)}

If the continuity between the juvenile-onset form and the adult form of bipolar disorder and the differing phenomenology can be firmly established, perhaps future generations of DSM should include a separate diagnostic entity of juvenile-onset bipolar disorder.

EPIDEMIOLOGY

Whereas ADHD is among the most common psychiatric disorders of childhood, occurring in 3% to 5% of school-aged children¹⁴ and accounting for approximately 40% of clinical referrals,¹⁵⁻¹⁷ bipolar disorder is thought to be rare in childhood. Beginning with Kraepelin in 1921, surveys have found that age at onset prior to 10 years occurs in only 0.3% to 0.5% of bipolar patients, and approximately 20% of adults with bipolar disorder report that symptoms began before the age of 19 years.¹⁸⁻²¹

The prevalence of bipolar disorder in adults is approximately 1%,²² which is thought to be a reliable estimate since this rate is remarkably consistent across time and cultural boundaries, and it seems likely that the significant impairment in functioning caused by bipolar disorder would lead to a high detection rate. If 4% of school-aged children are diagnosed with ADHD, and 22% of these have bipolar disorder, then the childhood prevalence of 0.88% would be close to the adult prevalence. Age-at-onset studies of bipolar disorder do not support the notion that most incidences begin in childhood, raising questions

about the accuracy of prevalence estimates and continuity between the childhood- and adult-onset forms.

Although less useful for the question of comorbidity during adolescence, age at onset can be very important for discriminating between bipolar disorder and ADHD, since ADHD by DSM-IV definition begins before 7 years of age.

FAMILY HISTORY

As both ADHD and bipolar disorder are heritable disorders,²³ careful assessment of family history is a crucial component of the clinical assessment. Studies assessing first-degree relatives of children with ADHD or combined bipolar disorder and ADHD found that the relatives of subjects who had combined bipolar disorder and ADHD had higher rates of both disorders, whereas the relatives of subjects who had only ADHD had higher rates of ADHD but not bipolar disorder.^{24,25} The rate of ADHD in relatives was not statistically different between the group with combined bipolar disorder and ADHD diagnoses and that with ADHD alone.

TREATMENT RESPONSE

Lithium, carbamazepine, and valproate are widely used as mood stabilizers in pediatric populations, although carbamazepine and valproate are not approved by the Food and Drug Administration (FDA) for bipolar disorder in children or adolescents, and lithium is approved only for adolescents older than 12 years. The lack of FDA approval does not necessarily reflect lack of safety or efficacy, but it does reflect a lack of controlled studies. There are no double-blind placebo-controlled studies of mood stabilizers for the treatment of bipolar disorder in prepubertal children. Adolescents with bipolar disorder are generally thought to respond similarly to adults in pharmacologic interventions, but direct evidence is sparse. One well-controlled study²⁶ established the efficacy of lithium for adolescents with bipolar disorder and secondary substance dependency.

The few pediatric studies that do exist, although hampered by small sample sizes and diagnostic heterogeneity, support the safety and efficacy of lithium,^{7,27-31} with better support for adolescent onset.²⁷ Weight gain, acne, and frequent urination are the most common side effects for adolescents, although lithium is generally well tolerated if adequate monitoring and follow-up are available. Bipolar disorder is generally thought to be less responsive to treatment in adolescents than adults.^{32,33}

For ADHD, hundreds of studies have supported the safety and efficacy of stimulants. The most commonly prescribed are methylphenidate, dextroamphetamine, and a combination of dextroamphetamine and amphetamine. Patients not responsive to one stimulant are frequently responsive to one of the others.

Mood stabilizers are generally not effective for the treatment of ADHD. Stimulants, the treatment of choice for ADHD, are similarly ineffective in the treatment of bipolar disorder and may in fact induce mania in some individuals. Clinically, nonresponsiveness or an atypical response to pharmacologic management of a disorder should raise suspicions of an incorrect diagnosis.

Selective serotonin reuptake inhibitors can cause activation that can be confused with mania or ADHD in children with bipolar disorder.

BRAIN IMAGING

Brain imaging, although currently not of diagnostic utility for either bipolar disorder or ADHD, may someday be useful for discriminating the disorders. There are 2 published brain imaging studies regarding pediatric bipolar disorder. One reports decreased total cerebral volume and increased frontal and temporal sulcal size.³⁴ The other reports subcortical focal signal hyperintensities at the time of the first manic episode.³⁵ Adult bipolar disorder imaging studies report temporal lobe, amygdala, and hippocampal changes,^{36–40} ventricular enlargement,^{41–43} cerebellar reductions,⁴⁴ and hyperintensities in various brain regions.^{42,45–47}

Areas of the brain reported to be anomalous in ADHD have included the corpus callosum,^{1,48–51} but consensus is most strong for a reduction in total brain volume,⁵² with preferential reduction of the frontal lobes,^{50,52} basal ganglia,^{52–55} and cerebellum.⁵⁶ As opposed to the progressive brain changes noted in childhood-onset schizophrenia,^{57,58} the brain changes in ADHD appear to be relatively static.

Although there is some overlap in areas of the cerebellum and basal ganglia, the brain imaging findings for the two disorders are quite divergent, especially for temporal and medial temporal regions that are affected in bipolar disorder but not ADHD.

DISCUSSION

The distinction between juvenile-onset bipolar disorder and ADHD can be challenging. Phenomenologically, juvenile-onset bipolar disorder is characterized by non-episodic, chronic, rapid-cycling, mixed manic states. Longitudinal studies are needed to address continuity with the adult form and to establish the developmental course of the illness.

Brain imaging studies are not currently of utility in differentiating the disorders, but the patterns of anomalies are distinct between the disorders, and imaging may be useful to differentiate or provide useful subtyping at some point in the future.

There is debate over the actual prevalence of youths meeting formal DSM-IV criteria for bipolar disorder, whether the juvenile-onset form should have separate diagnostic criteria, and whether “continuous” mania is com-

patible with the well-established distinct-episode phenomenology of adult bipolar disorder. Most clinicians would agree that mania-like disorders are commonly seen in juveniles, especially in inpatient settings, and that many of these patients may possibly benefit from mood-stabilizing medications.

Given the frequency with which mood-stabilizing agents are prescribed to pediatric populations, it is alarming that there are so few controlled studies to address safety and efficacy. With so few pediatric data available, clinicians rely on extrapolation from adult studies to guide treatment. This has proved problematic for the treatment of childhood depression, where, despite agreement that the disorder is continuous with the adult form, tricyclic antidepressants are not as effective for children as adults.⁵⁹ In light of imaging evidence indicating tumultuous changes in disease-relevant brain regions during normal adolescence,⁶⁰ differences in phenomenology or treatment response between children and adults, even if the childhood-onset and adult forms are continuous, is unsurprising. Clearly, more studies, including those with a longitudinal design, are needed to help guide clinicians through the difficult terrain of diagnosis and treatment of children with mania-like symptoms.

Drug names: carbamazepine (Tegretol and others), dextroamphetamine (Dexedrine and others), dextroamphetamine/amphetamine (Adderall), methylphenidate (Ritalin).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, carbamazepine and valproate are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder in juveniles.

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