

# Recognizing and Managing Bipolar Disorder in Children

Janet Wozniak, M.D.

Bipolar disorder affects people of all ages, including preschool-aged children. Two major difficulties in diagnosing children with bipolar disorder are its overlap with attention-deficit/hyperactivity disorder (ADHD) and its developmentally distinct presentation from that in adults, with high rates of irritability, chronicity, and mixed states. Comorbid conditions are common in bipolar disorder and, in addition to ADHD, include depression, anxiety disorders, oppositional defiant disorder, and conduct disorder. Family studies have helped to confirm the validity of bipolar disorder in children. In terms of treatment, children do not appear to respond well to conventional mood stabilizers alone. However, using an atypical antipsychotic either alone or in addition to another mood stabilizer has shown utility in treating manic symptoms, depression in mixed states, and aggression. Amphetamine salts have been helpful in treating bipolar children with comorbid ADHD, but no data are available on treating comorbid depression in bipolar children. Because childhood-onset mania is commonly chronic rather than episodic, highly comorbid, and characterized by high rates of irritability, future clinical trials should examine the overlap of mania with other disorders in children to determine routes to accurate diagnosis and treatment.

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Converging evidence suggests that bipolar disorder can commonly occur in very young children but may be difficult to diagnose. One of the main challenges of diagnosing bipolar disorder in children and adolescents is its high comorbidity with other psychiatric disorders, particularly attention-deficit/hyperactivity disorder (ADHD), conduct disorder, and depression. The overlap of bipolar disorder with ADHD has caused considerable confusion and debate in the child psychiatry field. ADHD is a common disorder affecting 5% to 7% of children,<sup>1</sup> but some of the core symptoms of ADHD, such as distractibility, physical hyperactivity, and talkativeness or pressured speech, directly overlap with the diagnostic criteria for mania. The other main challenge of diagnosing bipolar disorder in children and adolescents has been its distinct presentation from that commonly thought to occur in adults.

## OVERLAPPING ADHD AND OTHER PSYCHIATRIC DISORDERS

Many studies<sup>2-7</sup> have demonstrated that children and adolescents with a current diagnosis of mania or bipolar

disorder have symptoms that overlap with ADHD, a relationship that appears to be a function of age at onset of bipolar disorder. Among children 12 years old or younger, the overlap of bipolar disorder with ADHD appears almost universal (ranging from 73% to 98%).<sup>2,4,8</sup> In the adolescent-onset form of bipolar disorder (in adolescents  $\geq$  13 years old), the overlap is lower (ranging from 57% to 74%).<sup>4,5,8,9</sup>

Increasingly, adults are presenting with bipolar disorder comorbid with ADHD.<sup>3,10</sup> Some of these adults report an early age at onset of their bipolar disorder. For example, a recent report<sup>11</sup> of data from the first 1000 participants of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed that 20.4% of adults with very early onset bipolar disorder (onset when they were  $\leq$  13 years old) had comorbid ADHD and bipolar disorder. Even more adults date the start of their bipolar disorder to the adolescent years.<sup>12-14</sup> Overall, adults with an earlier age at onset and a higher level of comorbidity have worse functioning, which is similar to outcomes seen in children with bipolar disorder. Increasingly, adult data of combined bipolar disorder and ADHD have supported findings in children,<sup>15</sup> demonstrating that bipolar disorder plus ADHD may be a distinct genetic subtype and an important part of the heterogeneity of bipolar disorder in general.

Data over time and across centers have revealed a pattern of bipolar presentation in children that is remarkably consistent.<sup>2,8,16</sup> In our 1995 study,<sup>2</sup> for example, we reported that although children meeting diagnostic criteria for mania frequently met criteria for ADHD (98%), ADHD children less frequently met criteria for mania (20%).

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*From the Pediatric Psychopharmacology Unit, Massachusetts General Hospital, Boston.*

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*Corresponding author and reprints: Janet Wozniak, M.D., Pediatric Psychopharmacology Unit, Massachusetts General Hospital, 185 Alewife Brook Parkway, Suite 2000, Cambridge, MA 02138 (e-mail: jwozniak@partners.org).*

Table 1. Rates of Additional Psychiatric Disorders Found in Children With Mania and ADHD<sup>a</sup>

Psychiatric Diagnoses	Manic Children (N = 43)		ADHD Children (N = 164)		Non-ADHD Controls (N = 84)		Significance <sup>b</sup> (df = 2) p Value
	N	%	N	%	N	%	
Major depression	37	86 <sup>c,d</sup>	63	38 <sup>d</sup>	3	4	< .001
Psychosis	7	16 <sup>c</sup>	3	2	NA	0	< .001
Conduct disorder	16	37 <sup>c,d</sup>	24	15 <sup>d</sup>	0	0	< .001
Oppositional defiant disorder	38	88 <sup>c,d</sup>	78	48 <sup>d</sup>	3	4	< .001
Multiple anxiety disorders (≥ 2)	24	56 <sup>c,d</sup>	43	26 <sup>d</sup>	1	1	< .001
Overanxious disorder	21	49 <sup>c,d</sup>	39	24 <sup>d</sup>	2	2	< .001
Separation anxiety disorder	19	44 <sup>c,d</sup>	36	22 <sup>d</sup>	4	5	< .001
Agoraphobia	14	33 <sup>c,d</sup>	24	15 <sup>d</sup>	1	1	< .001
Panic disorder	4	9 <sup>c,d</sup>	1	0.6	0	0	< .001
Social phobia	10	23 <sup>d</sup>	26	16 <sup>d</sup>	1	1	< .001
Simple phobia	8	19	28	17	7	8	.138
Obsessive-compulsive disorder	5	12 <sup>d</sup>	7	4	0	0	.008
Tic disorders	11	26 <sup>d</sup>	49	30 <sup>d</sup>	5	6	< .001

<sup>a</sup>Reprinted with permission from Wozniak et al.<sup>2</sup>

<sup>b</sup>Overall comparisons between manic, ADHD, and non-ADHD control by  $\chi^2$  analyses or by analysis of variance.

<sup>c</sup> $p \leq .01$  versus ADHD by  $\chi^2$  analysis or by Fisher protected least significant difference.

<sup>d</sup> $p \leq .01$  versus non-ADHD control by  $\chi^2$  analysis or by Fisher protected least significant difference.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NA = not applicable.

Compared with children with ADHD without mania, children with ADHD and mania had more comorbid psychiatric disorders, such as depression, oppositional defiant disorder, and multiple anxiety disorders (Table 1).

Children with manic symptoms appear to have a high rate of depression.<sup>2</sup> About one third of children present with depression first, one third present with mania first, and about one third present with a mixed state (manic and depressed symptoms simultaneously apparent). Children with bipolar disorder not only have high rates of depression, they also tend to meet criteria for severe depression, with high rates of suicidality as well as suicide attempts, and often require hospitalization for suicidal behavior as well as their aggressive behaviors.<sup>17</sup> Data<sup>18</sup> on adolescent suicide show that those who completed suicide had higher rates of bipolar disorder, especially mixed states, and a higher rate of comorbid ADHD than those who attempted suicide.

Besides depression, children with mania also have a high rate of oppositional defiant disorder.<sup>2</sup> Parents of bipolar children with oppositional defiant disorder or conduct disorder report high rates of all symptoms to severe degrees.<sup>2,19</sup> ADHD has long been known as a risk factor for developing conduct disorder; in one study,<sup>20</sup> 50% of youths with ADHD met criteria for conduct disorder at a 1-year follow-up. But, in our study,<sup>2</sup> children with mania had a rate of current comorbid conduct disorder more than twice that of the ADHD children. Because conduct disorder is a precursor to later adult antisocial behaviors and criminality, children with bipolar disorder are an important group to study from a public health perspective. Children with bipolar disorder also have high rates of anxiety disorders,<sup>21,22</sup> a bidirectional overlap with obsessive-compulsive disorder,<sup>21,23</sup> and, although understudied, autism.<sup>24</sup>

## RECOGNIZING DEVELOPMENTALLY DISTINCT PRESENTATION

Age at onset of bipolar disorder in children varies widely and includes very young children ( $\leq 5$  years old). Although the average age of referral to our clinic is 8 years, about 75% of parents report symptoms beginning during the preschool years. Consequently, most children who eventually receive treatment have already suffered an average of 3 to 4 years with either no treatment or inappropriate treatment for their mood disorder. The increasing recognition among clinicians that parents are describing bipolar disorder in their preschool children has led to more attention being paid to identifying and treating the disorder in these very young patients. Clinicians who identify bipolar disorder in young children must rely heavily on case reports in the literature to determine appropriate treatment.<sup>25</sup> Research studies, especially treatment studies in such young patients, are difficult to conduct and often met with resistance.

Investigations into the developmentally distinct presentation of bipolar disorder in children as opposed to adults have focused on atypical presentation and the need for developmentally sensitive assessment tools. Investigations that focus on presentation report that children tend to have higher rates of mixed states, higher levels of irritability as the presenting mood complaint, more chronicity, and a complex cycling pattern that lacks a recovery period or interepisode high functioning.<sup>26,27</sup> This atypicality has led to some debate as to whether children are presenting with bipolar disorder as seen in adults.

Investigations that focus on assessment methods report a need for developmentally sensitive questions to uncover the core symptoms of mania or bipolar disorder in children. The lack of an assessment tool that culls childhood

traits from mood disorders may be one of the reasons that childhood bipolar disorder has been overlooked in the past. For example, the presence of mood reactivity, moodiness, or even grandiosity has been considered, in many cases, to be a normal trait of childhood because children have less of a capacity than adults for affective regulation. Thus, efforts to validate an instrument specific to pediatric bipolar disorder are underway,<sup>28</sup> and pediatric prompts for use with psychiatric rating scales such as the General Behavior Inventory<sup>29</sup> and the Young Mania Rating Scale<sup>30</sup> are being developed. For instance, questions regarding hypersexuality could include additional prompts to parents regarding their children: “Does your child exhibit excessive interest in sexual matters or bodily functions and private body parts (more than other children his or her age)?” “Does your child seek out pornography or sexual content in the supermarkets or on the Internet?” “Does your child touch himself or herself on the genitals in public or touch others inappropriately?” These questions often elicit responses from parents that reveal aspects of increased sexual interest and activity in children that may not have been linked to the mood disorder. Questions about grandiosity are also being expanded to help identify children who overestimate their ability to do things and take excessive chances or act excessively boastful or bossy in ways that alienate others. In some children, increased oppositional and defiant behaviors toward authority figures may represent the grandiosity of mania.

In a recent case study, Tumuluru et al.<sup>25</sup> reported that 6 preschool-aged children who met the criteria for severe mania were admitted to a children’s inpatient psychiatric unit. Irritability was readily observable but euphoric mood was not. Consistent with a previous report,<sup>31</sup> a strong family history of mood disorders as a predictor of bipolar illness was present in these preschool children. In addition, at some point, each child presented with ADHD symptoms and mood symptoms that impaired functioning similar to those found in older children. In another study, Wilens et al.<sup>32</sup> compared preschool-aged children and school-aged children in an outpatient psychopharmacology clinic and found that the younger children presented with all the same symptoms seen in the older children. These findings underscore the need for clinicians to overcome diagnostic prejudices and form developmentally sensitive questions that will help identify very young children with bipolar disorder.

At least one family study<sup>15</sup> confirms that mania presenting in children seems to be continuous with what we think of as bipolar disorder in adults. This study also confirms findings from a previous smaller pilot study<sup>10</sup> of 15 bipolar youths in 1995. This newer study<sup>15</sup> systematically assessed 107 manic children and adolescents with 298 first-degree relatives. Children who met criteria for mania had greater rates of familiarity of mania than comparison groups of ADHD or control children, 14% versus 4%.

About 40% to 50% of the manic children had a first-degree relative with bipolar disorder. This study also confirmed a pattern of cosegregation of bipolar disorder and ADHD, suggesting that combined bipolar disorder and ADHD may be a genetic subtype of bipolar disorder possibly with its own course, family history, and treatment responsiveness. In other studies,<sup>10,33</sup> children with comorbid ADHD and mania were found to have greater family history of mood disorder compared with non-bipolar disorder ADHD children. These findings indicate the need for more specific genetic studies in the future.

As child and adolescent psychiatry professionals have become aware of and accustomed to the fact that children can present with severe mood symptoms that suggest bipolar disorder, the question has arisen as to whether there are particular cardinal symptoms that are more useful than others in making the diagnosis, especially in cases that might appear to be borderline. Proposed criteria<sup>7,34</sup> that could be useful in discerning genetically distinct groups include euphoria versus irritability, grandiosity, and evidence of clear cycling or episodicity. These particular characteristics have been proposed because euphoria and grandiosity are thought by some clinicians to be unique to mania with no overlap with other disorders. Irritability, on the other hand, is a presenting feature of depression as well as other disorders such as oppositional defiant disorder. Although irritability is not one of the criteria for a diagnosis of ADHD, it is thought of as a common correlate of ADHD. Other groups<sup>35</sup> have argued that the irritability of mania appears to be qualitatively and quantitatively distinct and can be a useful symptom in discerning manic children.

Our research group recently presented data<sup>36</sup> suggesting that stratifying by these proposed cardinal features does not predict a more familial form of pediatric bipolar disorder. In addition, the proposed cardinal features did not predict any difference in symptom presentation, course, age at onset, or patterns of comorbidity. Whether cardinal symptoms will become important in making the diagnosis of childhood bipolar disorder or not remains to be decided.

## TREATING BIPOLAR DISORDER IN CHILDREN

### Mood Stabilizers

Treatment studies in bipolar children have expanded in the past several years. Generally, conventional mood stabilizers—lithium, valproic acid, or carbamazepine—have low effect sizes in bipolar children. Kowatch et al.<sup>37</sup> reported that only about 40% of children and adolescents taking lithium, carbamazepine, or valproic acid responded to these medications. Wagner et al.<sup>38</sup> found similar low effect sizes in children and adolescents taking divalproex sodium, including a high dropout rate owing to side effects or ineffective treatment. However, increasingly, studies have examined whether combination treatment with these

various agents may lead to better outcomes. Results from the second phase of the study by Kowatch et al.<sup>39</sup> indicated that combined treatment led to a better outcome than using any 1 of the medications on its own (regardless of which 2 therapies were combined). Studies of the combination of 2 mood stabilizers (lithium and divalproex sodium)<sup>40</sup> or a mood stabilizer and an atypical antipsychotic (lithium and risperidone<sup>41</sup> or valproic acid and quetiapine<sup>42</sup>) have demonstrated superior efficacy to traditional mood stabilizers used alone.

### Atypical Antipsychotics

Despite the lack of controlled trials in young patients, atypical antipsychotics, which have been found to have mood-stabilizing properties in adults, are increasingly used as first-line treatments in children and adolescents with bipolar disorder. Reasons for their increasing use include the observations that traditional mood stabilizers are associated with a long length of time required to stabilize bipolar children, difficulty in treating children with bipolar disorder,<sup>43</sup> the need for a large number of medications used in combination to stabilize youth, and high rates of relapse.<sup>44</sup> The atypical antipsychotics risperidone, olanzapine, quetiapine, and ziprasidone have been approved by the U.S. Food and Drug Administration (FDA) for use in adults with mania and are commonly utilized clinically in pediatric populations. In addition, the FDA recently approved aripiprazole for the treatment of acute bipolar mania, including manic and mixed episodes, in adults.

A chart review<sup>45</sup> of youths with DSM-IV bipolar disorder indicated a favorable response to risperidone. Of 28 juvenile patients who received risperidone, 82% showed improvement in mania and aggression, while 69% showed improvement in psychotic symptoms. Risperidone also demonstrated utility in reducing some of the depression presented in children with bipolar disorder in mixed states. Although a trial<sup>46</sup> of risperidone in children with subnormal IQ and conduct disorder did not specifically examine mood symptoms, a reanalysis<sup>47</sup> of this sample showed possible utility for mania and depression. These results lend support to the use of risperidone for pediatric mania. Olanzapine has shown utility for reducing manic symptoms in adults, and open research<sup>48</sup> has shown that olanzapine was useful in 20 bipolar children and adolescents. A multi-site, double-blind, placebo-controlled trial of olanzapine in adolescents with bipolar disorder is under way.

### Recommendation

The poor effect sizes and the need for combined treatments with the conventional mood stabilizers, as well as the more robust data that are starting to accumulate on the atypical antipsychotics, generally indicate that, in clinical settings, atypical antipsychotics should be considered first-line treatments for many cases of pediatric mania. Due to the substantial morbidity associated with pediatric-

onset bipolar disorder, all of the mood stabilizers that are used in adult bipolar disorder are commonly used in clinical settings to treat children and adolescents despite the current void of scientific evidence to demonstrate their utility.<sup>49</sup>

## TREATING COMORBID CONDITIONS

Treating comorbid conditions in young patients with bipolar disorder offers another challenge for clinicians. Little has been published on treating the ADHD symptoms that are frequently comorbid in children with bipolar disorder. A review<sup>50</sup> of our own patient charts showed that using ADHD medications in this group either made matters worse or had no effect if manic symptoms were not stabilized. However, after reducing manic symptoms in a bipolar child, adding treatment that is appropriate for ADHD can improve the complicated clinical picture. We found that the proportion of visits at which ADHD symptoms were rated as improved following initial improvement in manic symptoms was 7.5 times greater than before initial improvement of manic symptoms.

The clinical wisdom is to proceed with caution, but generally ADHD in and of itself carries so much morbidity that clinicians find themselves compelled to make attempts to treat the ADHD when the patient's mood is stable by adding a treatment for ADHD. Scheffer,<sup>51</sup> for example, showed that mixed amphetamine salts could be successfully used to treat ADHD in youth with comorbid ADHD and bipolar disorder after mood stabilization with divalproex sodium.

No studies of treating the depressive aspect of bipolar disorder in children exist. Given the morbidity associated with depression in bipolar disorder in adults and the recent concerns that have been raised regarding the serious side effects that can be associated with antidepressants in the pediatric population, treating depression in juveniles has become a matter of increasing concern.<sup>52</sup>

## CONCLUSION

The overlap of bipolar disorder with other psychiatric conditions is common and includes depression, anxiety disorders, oppositional defiant disorder, and conduct disorder. Even children as young as preschool age can suffer from bipolar disorder. Treating young children is difficult because of the large number of medications they need in combination and the high rates of relapse. However, atypical antipsychotics and combinations of mood stabilizers have been found in some preliminary studies to be effective in treating manic symptoms, depression in mixed states, and aggression. Amphetamine salts have been helpful in treating bipolar children with comorbid ADHD in one preliminary report,<sup>51</sup> but no data are available on treating comorbid depression in bipolar children. Future

clinical trials should examine treatments that may be useful for treating not only the manic symptoms of bipolar disorder, but also the depressive phase and mixed states in children and the overlap of bipolar disorder with other psychiatric disorders.

*Drug names:* amphetamine/dextroamphetamine (Adderall and others), aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others), ziprasidone (Geodon).

*Disclosure of off-label usage:* The author has determined that, to the best of her knowledge, aripiprazole, carbamazepine, divalproex, lithium, olanzapine, quetiapine, risperidone, valproic acid, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of pediatric bipolar disorder.

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