

# Diagnostic and Therapeutic Dilemmas in the Management of Pediatric-Onset Bipolar Disorder

Janet Wozniak, M.D.; Joseph Biederman, M.D.; and Jennifer A. Richards, B.A.

Although the diagnosis of pediatric-onset bipolar disorder is controversial, an increasing literature of systematic research has challenged the traditional view that this disorder is a rare condition. This article summarizes research regarding the atypical presentation of pediatric bipolar disorder and its overlap with attention-deficit/hyperactivity disorder and other comorbid conditions, as well as family-genetic and treatment data. When structured interview data were examined, cases of pediatric mania constituted 16% of referrals to our outpatient clinic. Presentation is atypical by adult standards and includes irritability, chronicity, and mixed state. Family-genetic and treatment data help to establish diagnostic validity. Pediatric bipolar disorder is not a rare condition. Treatment requires a combined pharmacotherapy approach to address issues of comorbidity. Atypical antipsychotic medications have provided promising treatment results, but additional controlled clinical trials are needed.

*(J Clin Psychiatry 2001;62[suppl 14]:10-15)*

The diagnosis of childhood-onset bipolar disorder has been met with skepticism by the clinical and research community, leading to a cycle of under-identification and reluctance to study or diagnose the condition despite the documented high levels of morbidity associated with its symptoms. Reasons for this state of affairs include the developmentally different presentation that children may have from the adult form of the disorder. Also, children with bipolar disorder frequently have symptoms of attention-deficit/hyperactivity disorder (ADHD), which may lead to the diagnosis of ADHD by the pediatric clinician well trained in the recognition of this disorder, but with neglect of the coexisting mood disorder.<sup>1-3</sup> Furthermore, given that adult ADHD has only recently gained attention from the clinical and research community, the comorbid condition of bipolar disorder and ADHD has been an “orphan diagnosis,” neglected by clinicians at both ends of the life cycle.

Recent work has established that, contrary to being uncommon, childhood-onset bipolar disorder may account for a significant number of child psychiatry referrals.<sup>4-7</sup> To test this hypothesis, rather than rely on clinician diagnosis, which could be affected by preexisting prejudice against the disorder, we looked at all of the structured interview-derived diagnoses (such as those derived from the Schedule for Affective Disorders and Schizophrenia for School Age Children) for children under 12 years of age referred to our outpatient pediatric psychopharmacology clinic over a 4-year period.<sup>8</sup> These were structured interviews with a parent (usually the mother) about the child, which form part of our routine evaluation procedure. This analysis yielded the finding that childhood-onset bipolar disorder made up 16% of the prepubertal referrals to our clinic, or 43/269 children.

## PRESENTATION OF MANIA

The children with bipolar disorder in our study<sup>8</sup> presented with an atypical clinical picture by adult standards with irritability, mixed presentation, and chronicity. Various authors have commented on this atypical presentation.<sup>7,9,10</sup> Ninety-two percent of parents indicated that irritability was the impairing mood state (Figure 1). While 17% of parents also indicated impairing levels of euphoria or elation, these giddy, “goofy,” silly, or “high” mood states were less impairing than the irritability and occurred in a smaller percentage of patients. In a current ongoing family study of childhood-onset mania that we are conducting, the majority of parents endorse a mixture of abnormal mood states, including irritability, euphoria, and depression, which occur during more than 75% of the day,

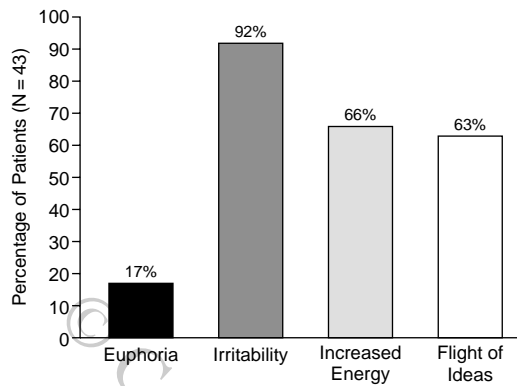
---

*From the Pediatric Psychopharmacology Unit of the Child Psychiatry Service, Massachusetts General Hospital, Harvard Medical School, Boston.*

*Supported in part by grant RO1 MH50657-05 from the National Institute of Mental Health, Bethesda, Md.; a grant from NARSAD; a small grant from the Massachusetts Mental Health Center and the Commonwealth Research Center; and a grant from the Theodore and Vada Stanley Foundation.*

*Presented at the symposium “The Role of Anticonvulsants as Mood Stabilizers,” which was held September 22, 2000, in San Antonio, Tex., and supported by an unrestricted educational grant from Glaxo Wellcome.*

*Reprint requests to: Janet Wozniak, M.D., Pediatric Psychopharmacology Unit, ACC 725, Massachusetts General Hospital, 15 Parkman St., Boston, MA 02114 (e-mail: wozniak@helix.mgh.harvard.edu).*

Figure 1. Frequency of Bipolar Symptoms<sup>a</sup>

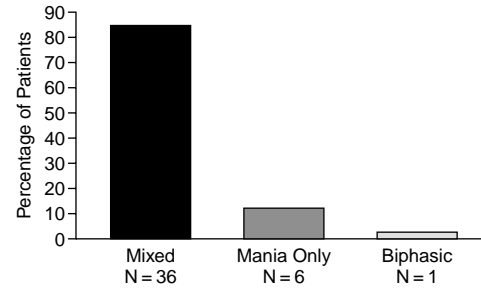
<sup>a</sup>Data from Wozniak et al.<sup>8</sup>

more days than not, with irritability generally representing the most impairing mood state.

While irritability can be a common characteristic in children, parents are able to describe varying degrees and intensities of this symptom. Children without a psychiatric diagnosis can demonstrate grouchy, cranky moods from time to time. Children with ADHD may have higher levels of irritability due to the frustration associated with inattention, distractibility, and impulsivity. Children with depression can have irritability as a developmentally distinct form of the disorder, rather than classic melancholy.<sup>11</sup> The depressive type of irritability is characterized by unhappy, hard-to-please, cranky moods and is more severe and pervasive than either age-appropriate irritability or the irritability commonly thought to occur with ADHD. Furthermore, depressive irritability is more likely to be associated with expressions of self-hatred, low self-esteem, and self-destructive statements and actions.

In contrast, the irritability associated with mania has a much more hostile, vicious, attacking quality.<sup>12</sup> In addition to a general level of irritability, manic children also present with extremely impairing dysphoric, explosive episodes, which generally occur daily with little or no precipitant. These explosions can last up to an hour or longer and may involve destruction of property such as kicking holes in walls and throwing and breaking household items. During these rages, children are hard to calm and often lash out physically at those around them with kicking, hitting, biting, or spitting. Swearing and hostile comments are also common. Parents almost universally say they “walk on eggshells” out of fear of these unpredictable outbursts.

Euphoric moods are generally elicited by inquiring for giddy, “goofy,” hyperexcited, or silly states with laughing fits. Parents will describe that the child acts in an immature, clownish manner to the extent of alienating those around him or her. Grandiosity or flight of ideas can occur in these or the irritable states. Because grandiosity is a normal trait of childhood and adolescence, it may be difficult

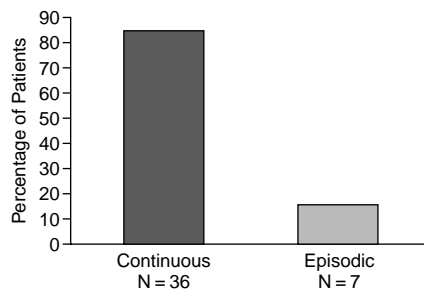
Figure 2. The Mixed Presentation of Childhood Mania<sup>a</sup>

<sup>a</sup>Data from Wozniak et al.<sup>8</sup>

for clinicians to discern a psychopathologic state of grandiosity.<sup>5</sup> Parents may not complain of grandiosity, finding the trait amusing or cute in the children. For example, one parent proudly described his child’s letters to Steven Spielberg, the famous director, about movie ideas. Another parent noted his child’s mechanical abilities and plan to build a computer. One child began to dig up the backyard to plant a garden to feed the starving people in the world. Another child developed the nickname “Mr. Hollywood.” Another took it upon himself to “correct” his teacher during lectures. Grandiosity can also take the form of acting “like an adult.” Parents say the children act “too big for their britches,” in a bragging or bossy manner, or that they “rule the roost” to a psychopathologic extent.<sup>5</sup>

Parents will also describe their children as having an extreme degree of grandiose defiance, reporting to adults “I know better” and refusing to comply with authority at home or at school. Children with bipolar disorder almost universally have comorbid oppositional defiant disorder, in a very severe form. As opposed to developmentally appropriate defiant states, or the increased oppositionality seen in children with ADHD, the defiant state in childhood bipolar disorder has a grandiose quality that creates problems at home, in school, and in sports or other activities. Children will believe themselves to “know better” than adults around them and on this basis refuse to comply with what they see as petty or “stupid” demands on them. These children are often labeled as having “an attitude problem” and inspire the anger of adults.

Little is known about the variations between bipolar and unipolar depression in children and adolescents. In our sample of children meeting criteria for mania,<sup>8</sup> 90% have also had a depressive episode, and 84% have had the depressive episode overlap in time with the manic episode, representing a mixed state (Figure 2). This is usually described as children switching in and out of depression, irritable mania with explosions, and euphoric “silly” mania unpredictably throughout the day, almost every day, with very little time spent in a regular age-appropriate mood state. One article<sup>13</sup> described this state as ultradian rapid cycling. Because of the switching among these mood

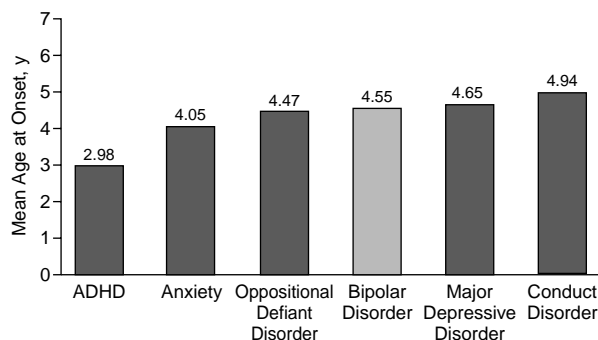
Figure 3. The Chronic Course of Mania in Children<sup>a</sup>

<sup>a</sup>Data from Wozniak et al.<sup>8</sup>

states, it is very difficult for some parents to agree that the child has had a “full week of irritability” or a “full week of euphoria” as required by some clinicians. On the other hand, parents describe periods of a mix of abnormal mood states spanning years with little normalcy, that is, a chronic state (Figure 3). A better characterization of childhood-onset mania, then, would be abnormal moods that present almost every day, during most of the day, for a majority of the time.

Despite this sort of chronicity, these children are also characterized by mood reactivity. Thus, a clinician may not see the abnormal moods in the same way as described by the parent, decreasing in utility the in-office mental status examination. Teachers, too, may see a different facet of the child’s mood. In our experience, only in the minority of the most severe cases do children demonstrate their most abnormal mood states at school or in the outpatient clinician’s office, although teachers generally report some sort of disruptive or moody behaviors. In the ongoing family study of pediatric mania at our center, approximately 20% of the nearly 60 patients seen in consultation exploded or demonstrated their severe irritability during the assessment process. This may be understood by thinking of these children the way we do adult individuals with bipolar II disorder, who may continue to function relatively normally in certain work or college settings, but clearly have abnormal and impairing mood states elicited while obtaining history. Another possibility is that many of these children may be conceptualized as having a disorder in formation, not yet in its most severe and constant form.

Another atypical feature of childhood-onset mania is the onset. If clinicians require that manic children present with a change from a previously high level of functioning, many cases will be missed. Of the children with the abnormal mood states noted above,<sup>8</sup> the mean age at onset of the manic syndrome was 4.55 years (Figure 4). This is distinct in time from the mean age at onset of ADHD in these same children, which was 2.98 years. An alarmingly large number of parents, greater than 75%, described the children’s mood symptoms as beginning under age 5, in the preschool years. A sizable subgroup of 25% of parents could

Figure 4. The Developmental Course of Bipolar Disorder in Children<sup>a</sup>

<sup>a</sup>Data from Wozniak et al.<sup>8</sup> Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

not pin down an age at onset, but felt that the child had “always” had an abnormal mood, even by infant standards.

### COMORBIDITY WITH ADHD

Of the 43 children under age 12 referred to our clinic who met criteria for mania,<sup>8</sup> 42, or 98%, also met criteria for ADHD. In contrast, 79% of referrals to our clinic met criteria for ADHD without mania.<sup>14</sup> Because mania and ADHD share 3 symptoms—talkativeness, distractibility, and physical hyperactivity/agitation—and since ADHD without mania is a much more common condition than ADHD with mania, it may be difficult to determine which children with ADHD also have mania. This could lead to the inappropriate administration of stimulant medication or anti-ADHD antidepressants that could exacerbate the mania.

We<sup>15</sup> also found that 76% of children with mania still retained full or subthreshold diagnostic status even when overlapping symptoms were subtracted from the algorithm; that is, children generally met criteria for mania robustly. Studies that attempt to distinguish manic children from children with ADHD note that manic children generally have greater psychopathology and poorer functioning.<sup>16</sup> Manic children, versus children with ADHD, have statistically significant lower Global Assessment of Functioning scores and statistically significantly higher scores on the Child Behavior Checklist subscales of aggression, psychosis, and anxiety/depression.<sup>17</sup> If ADHD rating scales are used, a manic child and a child with ADHD cannot be distinguished from each other. However, if an instrument such as the Mania Rating Scale is used, which asks questions about the symptoms specific to mania, manic children can be identified.<sup>18</sup> In general, it is important to note that ADHD criteria do not include a mood component. Thus, if the chief complaint or presenting symptom on examination is “severe moodiness,” a mood disorder diagnosis should be considered.

While it is important to recognize mania in a child with ADHD, it is also important to recognize ADHD in a manic child when it is present. The ADHD syndrome itself poses considerable suffering and morbidity. ADHD without mania is associated with poor functioning, higher levels of comorbidity with learning disabilities, and increased levels of conduct disorder and substance abuse.<sup>19</sup> Children with mania plus ADHD present with the neuropsychiatric correlates of ADHD, that is, high rates of learning disabilities and need for educational services. In a child with mania plus ADHD whose mood is well stabilized, ADHD symptoms often become the second most severe presenting complaint.<sup>20</sup> If the comorbid condition is not considered, the ADHD symptoms of inattentiveness, distractibility, talkativeness, and impulsivity might be mistaken for residual mania.

### **BIDIRECTIONAL OVERLAP BETWEEN ADHD AND BIPOLAR DISORDER**

In a well-characterized sample of boys with ADHD followed longitudinally,<sup>2</sup> analysis of structured interview data revealed that at ascertainment, 12% (N = 12) of the sample met criteria for mania. At follow-up 4 years later, an additional 12% had developed mania. Thus, while 98% of manic youth also had ADHD, 22% of youth with ADHD met criteria for mania, representing a bidirectional but asymmetrical overlap between mania and ADHD. When looking through the lens of ADHD, this overlap has led to the consideration that childhood-onset mania represents a severe form of ADHD or a subset of the ADHD population with severe moodiness.

In this sample,<sup>2</sup> baseline measures of boys who went on to develop mania during the follow-up period found rates of oppositional defiant disorder, conduct disorder, major depression, and anxiety disorders higher than those in boys who did not develop mania and similar to those seen in the boys with mania at baseline.

### **ADOLESCENTS WITH BIPOLAR DISORDER**

Because the children under 12 years presented with features of mania considered atypical by adult standards, we next analyzed data on the adolescents in our clinic, asking whether they would appear more classical in their presentation.<sup>14</sup> In fact, very few differences were found between adolescents with adolescent-onset mania, adolescents with childhood-onset mania, and children under 12 years of age with mania. Adolescents had a slightly higher rate of euphoria, but generally presented with impairing degrees of irritability and explosiveness, a chronic course, and mixed presentation.

However, the groups did differ in terms of rates of comorbid ADHD. Whereas the children under 12 years had almost universal comorbidity with ADHD, the adolescents

with adolescent onset of the disorder had a 60% rate of ADHD, consistent with levels of comorbidity seen in other samples of adolescents with bipolar disorder. This led to the conclusion that comorbidity with ADHD might be a marker for very early onset bipolar disorder. When looking through the lens of bipolar disorder, this overlap has led to the consideration that childhood-onset mania represents a severe form of bipolar disorder or a subset of the bipolar disorder population with severe ADHD and an early onset.

Although these data on adolescents provide additional evidence establishing the validity of the diagnosis of pediatric mania, longitudinal studies of children and adolescents into adulthood are still needed to confirm the findings.

### **FAMILY-GENETIC DATA**

In cases of diagnostic confusion between 2 disorders, or when elucidation of the relationship between 2 disorders is desired, family-genetic studies can be very helpful. In a pilot family study of children with bipolar disorder plus ADHD,<sup>21</sup> we found that first-degree relatives had higher rates of ADHD, major depressive disorder, and bipolar disorder than either the relatives of nonmanic ADHD probands or the relatives of controls. In addition, a pattern of cosegregation between bipolar disorder and ADHD was noted; that is, nearly all relatives with bipolar disorder also had comorbid ADHD. In other words, the combined condition of bipolar disorder plus ADHD seen in the proband was also seen in first-degree relatives, suggesting that bipolar disorder plus ADHD represents a distinct genetic subtype of either ADHD or bipolar disorder.<sup>22</sup>

### **OTHER COMORBID CONDITIONS**

In addition to ADHD, children with bipolar disorder have high levels of comorbidity with conduct disorder, anxiety disorders, and substance use disorders. Conduct disorder is a severe condition both from an individual as well as a public health perspective, as it represents early antisocial behavior, and many of these youngsters come to the attention of the criminal justice system. Various reports have documented an overlap between bipolar disorder and conduct disorder, noting that the comorbid condition heralds a more complicated course. Family-genetic work comparing rates of mania, antisocial disorders, and the combined condition in relatives of probands stratified by the presence or absence of these disorders revealed high rates of conduct/antisocial personality disorder in the relatives. Further analysis demonstrated the presence of 2 types of conduct/antisocial personality disorder in the relatives of children with conduct disorder and mania: with mania ("dysphoric conduct disorder") and without mania.<sup>23-26</sup> The issue is clinically an important one: when an irritable and grandiose youngster with mania lies, steals, or vandalizes, is it due to the disinhibition of the manic state

or is it due to a coexisting antisocial personality? In such cases, if the mania is well treated, would the conduct problems improve? The answers to these questions, not fully known, could determine whether such a child should be treated in the mental health system or enter the criminal justice system.

Another area of comorbidity is with anxiety disorders. A growing literature suggests that bipolar disorder in adults and children is highly comorbid with anxiety disorders. In our own work,<sup>27</sup> we have documented that 52% of children with anxiety disorders also have bipolar disorder. Furthermore, 56% of children with bipolar disorders present with multiple anxiety disorders (2 or more). Given these high rates of overlap, children with bipolar disorder should routinely be screened for anxiety disorders.

A growing literature suggests that juvenile-onset mania may be an important risk factor for substance use disorders. In particular, Wilens and colleagues<sup>28</sup> have demonstrated that individuals with adolescent-onset mania carry a particularly high risk for developing substance use disorders. More work is needed to understand the developmental relationship between substance use and mood dysregulation in adolescents, especially focusing on early intervention in the treatment of youth with mania as a way of preventing later substance use disorders.

### TREATMENT ISSUES

A small literature has addressed the use of mood-stabilizing medications (valproic acid, carbamazepine, lithium carbonate) in children and adolescents; however, much of this literature is limited by the lack of controlled clinical trials.<sup>29-33</sup> Furthermore, due to skepticism associated with the diagnosis of juvenile bipolar disorder, with few exceptions most of this literature addresses symptoms of conduct disorder or aggression and does not ascertain the presence of bipolar disorder in subjects. It is possible that the positive outcomes in some of these studies are due to the antimanic effects of the medications that treat the aggression and impulsivity of bipolar disorder.

Biederman et al.<sup>34</sup> systematically reviewed the clinical records of all pediatrically referred patients who at initial intake satisfied diagnostic criteria for mania based on a structured diagnostic interview with the mother. This chart review approach, starting with a diagnosis rather than reviewing the use of a particular treatment, offers the advantage of including all children with mania and examining our "naturalistic" clinical experience in treating them. We found that mood stabilizers were frequently used in these children and that their use was associated with significant improvement of the symptoms of mania. In contrast, antidepressants and stimulants were not associated with improvement of mania. For both lithium carbonate and carbamazepine, higher doses and blood levels predicted greater clinical improvement. However, time to response

was slow, requiring follow-up over a year or more, and the relapse rate in this population was high. These findings were consistent with other naturalistic outcome studies of bipolar children and adults in the literature.<sup>35,36</sup>

The advent of the atypical antipsychotics has provided an alternative treatment for this difficult-to-treat population, with a favorable side effect profile and improved efficacy. In a retrospective chart review of 28 children and adolescents with bipolar disorder treated with risperidone,<sup>37</sup> 82% of subjects improved in manic and aggressive symptoms. These youths improved relatively quickly, and average time to optimal response was approximately 2 months. No serious adverse events were observed. Furthermore, in an 8-week open study of olanzapine monotherapy in 23 children and adolescents,<sup>38</sup> significant improvement was noted in both symptoms of mania and depression with doses ranging from 2.5 to 20 mg/day. Furthermore, olanzapine was well tolerated.<sup>38</sup> These results are consistent with a recent report that risperidone was effective in managing aggression in children with conduct disorder.<sup>39</sup>

While the results associated with these studies of the atypical antipsychotic medications are promising, there is a continued need for additional short- and long-term controlled trials of mood-stabilizing medications of all classes in the treatment of pediatric bipolar disorder. While the atypical antipsychotics are well tolerated, weight gain and the possible risk of tardive dyskinesia limit the utility of these medications.

Because childhood-onset bipolar disorder is a highly comorbid condition, in addition to treating the symptoms of mania, most subjects will require a combined pharmacotherapy approach.<sup>20</sup> Our chart review suggests that symptoms of ADHD were stabilized only in subjects whose symptoms of mania were well treated. Thus, when designing a program of pharmacotherapy for an individual with both bipolar disorder and ADHD, medications for ADHD must be included and sequenced after the mood-stabilizing medications have effectively treated symptoms of mania. In addition, individuals may require medications for treatment of symptoms of depression and/or anxiety, also sequenced after the treatment of mania. Because additional medications for ADHD and depression may activate mania, these agents must be used cautiously, watching for exacerbation of mood instability.

### CONCLUSION

In summary, pediatric-onset bipolar disorder may account for a sizable portion of child psychiatry referrals. The syndrome shares symptoms with ADHD, and the differential diagnosis can be difficult. The condition appears to be insidious in onset, mixed with depression, and chronic, but characterized by mood reactivity. Irritability rather than euphoria may be the presenting complaint. Thus, by adult standards, childhood-onset mania may be

considered atypical in its presentation. Longitudinal studies of pediatric mania patients “grown-up” are needed to help confirm the validity of the diagnosis. A small literature suggests that the atypical antipsychotics are most uniquely effective in stabilizing symptoms of pediatric-onset mania. Finally, a combined pharmacotherapy approach is often necessary to address the complicated, highly comorbid clinical picture.

*Drug names:* carbamazepine (Tegretol and others), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

## REFERENCES

- Biederman J. Resolved: mania is mistaken for ADHD in prepubertal children. *J Am Acad Child Adolesc Psychiatry* 1998;37:1091–1093
- Biederman J, Faraone SV, Mick E, et al. Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? *J Am Acad Child Adolesc Psychiatry* 1996;35:997–1008
- Akiskal HS, Downs J, Jordan P. Affective disorders in referred children and younger siblings of manic-depressives: mode of onset and prospective course. *Arch Gen Psychiatry* 1985;42:996–1003
- Faadda G, Baldessarini R, Suppes T, et al. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. *Harv Rev Psychiatry* 1995; 3:171–195
- Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry* 1997;36:1168–1176
- Weller RA, Weller EB, Tucker SG, et al. Mania in prepubertal children: has it been underdiagnosed? *J Affect Disord* 1986;11:151–154
- Weller E, Weller R, Fristad M. Bipolar disorder in children: misdiagnosis, underdiagnosis, and future directions. *J Am Acad Child Adolesc Psychiatry* 1995;34:709–714
- Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 1995;34:867–876
- Carlson GA. Bipolar affective disorders in childhood and adolescence. In: Cantwell DP, Carlson GA, eds. *Affective Disorders in Childhood and Adolescence*. New York, NY: Spectrum Publications; 1983:61–83
- Ballenger JC, Reus VI, Post RM. The “atypical” picture of adolescent mania. *Am J Psychiatry* 1982;139:602–606
- Biederman J, Spencer T. Depressive disorders in childhood and adolescence: a clinical perspective. *J Child Adolesc Psychopharmacol* 1999;9: 233–237
- Davis RE. Manic-depressive variant syndrome of childhood: a preliminary report. *Am J Psychiatry* 1979;136:702–706
- Geller B, Cook EH Jr. Ultradian rapid cycling in prepubertal and early adolescent bipolarity is not in transmission disequilibrium with val/met COMT alleles. *Biol Psychiatry* 2000;47:605–609
- Faraone SV, Biederman J, Wozniak J, et al. Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry* 1997;36:1046–1055
- Milberger S, Biederman J, Faraone SV, et al. Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. *Am J Psychiatry* 1995;152:1793–1800
- Nieman GW, DeLong R. Use of the personality inventory for children as an aid in differentiating children with mania from children with attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 1987;26:381–388
- Biederman J, Wozniak J, Kiely K, et al. CBCL clinical scales discriminate prepubertal children with structured-interview derived diagnosis of mania from those with ADHD. *J Am Acad Child Adolesc Psychiatry* 1995;34: 464–471
- Fristad MA, Weller EB, Weller RA. The Mania Rating Scale: can it be used in children? a preliminary report. *J Am Acad Child Adolesc Psychiatry* 1992;31:252–257
- Biederman J, Keenan K, Faraone SV. Attention deficit hyperactivity disorder: family-genetic risk factors and comorbidity. In: Amir N, Branski D, eds. *Pediatric Neurology: Behavior and Cognition of the Child With Brain Dysfunction*, 1. Jerusalem, Israel: Basel, Karger; 1991:70–94
- Wozniak J, Biederman J. A pharmacological approach to the quagmire of comorbidity in juvenile mania. *J Am Acad Child Adolesc Psychiatry* 1996;35:826–828
- Wozniak J, Biederman J, Mundy E, et al. A pilot family study of childhood-onset mania. *J Am Acad Child Adolesc Psychiatry* 1995;34:1577–1583
- Faraone SV, Biederman J, Mennin D, et al. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry* 1997;36:1378–1387; discussion 1387–1390
- Biederman J, Faraone SV, Milberger S, et al. Is childhood oppositional defiant disorder a precursor to adolescent conduct disorder? findings from a four-year follow-up study of children with ADHD. *J Am Acad Child Adolesc Psychiatry* 1996;35:1193–1204
- Biederman J, Faraone S, Hatch M, et al. Conduct disorder with and without mania in a referred sample of ADHD children. *J Affect Disord* 1997;44: 177–188
- Biederman J, Faraone SV, Chu MP, et al. Further evidence of a bidirectional overlap between juvenile mania and conduct disorder in children. *J Am Acad Child Adolesc Psychiatry* 1999;38:468–476
- Wozniak J, Biederman J, Faraone SV, et al. Heterogeneity of conduct disorder: further evidence of a subtype of conduct disorder linked to bipolar disorder. *J Affect Disord*. In press
- Biederman J, Faraone SV, Marris A, et al. Panic disorder and agoraphobia in consecutively referred children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1997;36:214–223
- Wilens T, Biederman J, Millstein R, et al. Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 1999;36:680–685
- DeLong GR, Nieman GW. Lithium-induced behavior changes in children with symptoms suggesting manic-depressive illness. *Psychopharmacol Bull* 1983;19:258–265
- Cueva J, Overall J, Small A, et al. Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 1996;35:480–490
- Kowatch RA, Suppes T, Carmody TJ, et al. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2000;39:713–720
- Donovan SJ, Stewart JW, Nunes EV, et al. Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. *Am J Psychiatry* 2000;157:818–820
- Keck PE Jr, McElroy SL, Strakowski SM. Anticonvulsants and antipsychotics in the treatment of bipolar disorder. *J Clin Psychiatry* 1998; 59(suppl 6):74–81
- Biederman J, Mick E, Bostic JQ, et al. The naturalistic course of pharmacologic treatment of children with maniclike symptoms: a systematic chart review [CME]. *J Clin Psychiatry* 1998;59:628–637
- DeLong GR, Aldershof AL. Long-term experience with lithium treatment in childhood: correlation with clinical diagnosis. *J Am Acad Child Adolesc Psychiatry* 1987;26:389–394
- Strober M, Schmidt-Lackner S, Freeman R, et al. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. *J Am Acad Child Adolesc Psychiatry* 1994;34:724–731
- Frazier JA, Meyer MC, Biederman J, et al. Risperidone treatment for juvenile bipolar disorder: a retrospective chart review. *J Am Acad Child Adolesc Psychiatry* 1999;38:960–965
- Frazier J, Biederman J, Wilens T, et al. Advanced issues in psychopharmacology: psychotic disorders and bipolar disorders in children and adolescents. Presented at the 46th annual meeting of the American Academy of Child and Adolescent Psychiatry; 1999; Chicago, Ill
- Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. *J Am Acad Child Adolesc Psychiatry* 2000;39:509–516