Bipolar Disorder and Comorbid Anxiety Disorders in Children and Adolescents

Karen Dineen Wagner, M.D., Ph.D.

Recent attention has focused on the association between bipolar disorder and comorbid anxiety disorders in children and adolescents. There is a high rate of comorbidity between bipolar disorder and anxiety disorders in children and youths. Often, a child or adolescent with bipolar disorder has multiple comorbid anxiety disorders. In general, anxiety disorders precede the development of bipolar disorder in children. Comorbid disorders may worsen the course of each individual disorder. Pharmacologic management of the comorbid anxiety disorder is complicated by potential mood destabilization in a child or adolescent with bipolar disorder. *(J Clin Psychiatry 2006;67[suppl 1]:16–20)*

Bipolar disorder in children and adolescents is a serious illness with a chronic course. Geller et al.[1] reported that approximately 87% of children with bipolar disorder recovered from this illness within 48 months; however, 64% of the children relapsed after recovery. Psychosocial functioning is severely impaired in children with bipolar disorder.[2]

Comorbid disorders affect the course of bipolar illness in youth. For example, it is known that children with bipolar disorder and comorbid attention-deficit/hyperactivity disorder (ADHD) have a more severe clinical condition (e.g., more psychiatric hospitalizations and school failure) than children without comorbid ADHD.[3]

Recently, there has been increased interest in examining the association between bipolar disorder and comorbid anxiety disorders in children and adolescents.

EPIDEMIOLOGY

In a community sample of adolescents with bipolar disorder (I or II) and cyclothymia, aged 14 to 18 years, the lifetime prevalence rate for anxiety disorders was 33%.[4] In a sample of adolescents with subthreshold bipolar disorder (below the cutoff for the full syndrome), 29.3% had an anxiety disorder.[5] The rates of anxiety disorders in a community sample of adolescents with manic symptoms have been reported to be as high as 50%.[6]

The prevalence of anxiety disorders in prepubertal and early-onset adolescent bipolar I disorder in clinical settings was found to be 22.6%.[7] In this sample of youths with bipolar disorder, the rate of subsyndromal anxiety disorders was 45.2%. In a sample of clinically referred children with bipolar I disorder, the rate of anxiety disorders in preschoolers (4 to 6 years old) was 70% and in school-aged children (7 to 9 years old) was 76%.[8]

In contrast to these findings, Findling et al.[9] found a relatively low rate (14.4%) of anxiety disorders in children and adolescents with bipolar I disorder. These investigators surmised that the low rate of anxiety disorders may be due to the fact that, in their sample, only those youths who had symptom criteria for an anxiety disorder during periods of euthymia were diagnosed with a comorbid anxiety disorder.

High rates of anxiety disorders in adults have been associated with an earlier age at onset of bipolar disorder. Subjects (N = 938) who participated in the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder were assessed to determine the age at onset of their mood symptoms.[10] For those individuals who had a very early age at onset (< 13 years) of bipolar disorder, the prevalence rate of a comorbid anxiety disorder was 69.2%. For those individuals with an early age at onset (13 to 18 years old) of bipolar disorder, the prevalence rate of an anxiety disorder was 53.9%. Individuals with a later age at onset (> 18 years) of bipolar disorder had a prevalence rate of an anxiety disorder of 38.3%.

COMORBID OBSESSIVE-COMPULSIVE DISORDER

The clinical aspects of comorbid obsessive-compulsive disorder and bipolar disorder were investigated in a sample of 102 clinically referred children and adolescents over a 3-

From the Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston.

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Corresponding author and reprints: Karen Dineen Wagner, M.D., Ph.D., Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston, TX 77555-0188 (e-mail: kwagner@utmb.edu).

year period.[11] The mean age of the sample was 14.2 years. Thirty-seven patients (36.3%) were diagnosed with bipolar disorder, 35 patients (34.3%) were diagnosed with obsessive-compulsive disorder, and 30 patients (29.4%) were diagnosed with comorbid bipolar and obsessive-compulsive disorder. The age at onset of bipolar disorder was similar in the bipolar disorder group (11.8 years) and the comorbid bipolar and obsessive-compulsive disorder group (11.5 years). However, the age at onset of obsessive-compulsive disorder was significantly earlier in the comorbid bipolar and obsessive-compulsive disorder group (8.7 years) than in the obsessive-compulsive disorder group (11.3 years). The severity of illness was examined both at baseline and at 3-year follow-up. It was found that the severity of illness was significantly worse in the comorbid bipolar and obsessive-compulsive disorder group than in the group with obsessive-compulsive disorder at baseline. The severity of illness was similar for the bipolar disorder group and comorbid bipolar and obsessive-compulsive disorder group at baseline. At the end of follow-up, the severity of illness was significantly higher in the bipolar disorder group and comorbid bipolar and obsessive-compulsive disorder group than in the obsessive-compulsive disorder group.

In a sample of 30 consecutive referrals to a specialized pediatric obsessive-compulsive disorder clinic, 27% of the sample met criteria for comorbid mania.[12] The mean age at onset of bipolar disorder was 9 years, and the mean age at onset of obsessive-compulsive disorder was 8.5 years.

In a sample of 43 children and adolescents with bipolar disorder (I or II), 26 (44.2%) of the sample had comorbid obsessive-compulsive disorder.[13] Comorbid obsessive-compulsive disorder was found in 23 (24.7%) of 93 children with a diagnosis of bipolar I disorder.[7] For 114 children with mania, 16 (14%) had comorbid obsessive-compulsive disorder.[14] Comorbid obsessive-compulsive disorder was identified in 22 (48.9%) of 45 children with bipolar disorder (I or II).[15]

In a sample of clinically referred preschoolers with bipolar disorder (N = 44), 4 (9%) had comorbid obsessive-compulsive disorder. Among school-aged children with bipolar disorder (N = 29), 3 (10%) had comorbid obsessive-compulsive disorder.[8]

Although most studies have reported high rates of comorbid obsessive-compulsive disorder in children with bipolar disorder, Reddy et al.[16] found that only one child had bipolar disorder in a clinical sample of 54 youths in India with obsessive-compulsive disorder. Similarly, Leonard et al.[17] found only 1 case of bipolar disorder in a sample of 54 children with obsessive-compulsive disorder who were followed over a 2- to 7-year period.

COMORBID SOCIAL PHOBIA

Comorbid social phobia was found in 17 (39.5%) of 43 children and adolescents with bipolar disorder.[13] In a sample of 93 children and early adolescents with bipolar disorder, 3 (3.2%) were diagnosed with comorbid social phobia.[7] In 45 children and adolescents with bipolar disorder, comorbid social phobia was found in 15 (33.3%).[15] Comorbid social phobia was identified in 27 (24%) of 114 children with mania.[14]

Of 44 preschoolers with bipolar disorder, comorbid social phobia was found in 6 (14%). Of 29 children aged 7 to 9 years with bipolar disorder, comorbid social phobia was identified in 6 (21%).[8]

COMORBID GENERALIZED ANXIETY DISORDER

The comorbidity of generalized anxiety disorder was assessed in clinically referred children and adolescents.[18] The sample consisted of 157 outpatients, aged 7 to 18 years, with a diagnosis of generalized anxiety disorder. Eighteen patients (11%) of the sample had bipolar disorder; of those, 6 were children and 12 were adolescents. The highest rates of bipolar disorder (33.3%) were found for those youths with generalized anxiety disorder and comorbid externalizing disorders (ADHD, conduct disorder, and oppositional defiant disorder).

In a sample of 43 outpatient children and adolescents with bipolar disorder (I or II), 8 children (18.6%) had comorbid generalized anxiety disorder.[13] Comorbid generalized anxiety disorder was found in 12 (12.9%) of 93 children and adolescents with a diagnosis of bipolar I disorder.[7] In 45 children with bipolar disorder (I or II), 10 (20.4%) had comorbid generalized anxiety disorder.[15]

COMORBID SEPARATION ANXIETY DISORDER

In 114 clinically referred children with mania, 48 (42%) had separation anxiety disorder.[14] Separation anxiety disorder was diagnosed in 7 (16.3%) of 43 children and adolescents with bipolar disorder.[13] Tillman et al.[7] found that 16 (17.2%) of 93 children and early adolescents with bipolar disorder had comorbid separation anxiety disorder. Of 45 children and adolescents with bipolar disorder, 6 (13.3%) were found to have comorbid anxiety disorder.[15]

Comorbid separation anxiety disorder was found in 25 (57%) of 44 preschoolers with bipolar disorder. For children aged 7 to 9 years with bipolar disorder, 14 (48%) of 29 had comorbid separation anxiety.[8]

COMORBID PANIC DISORDER

Comorbid disorders were assessed in a sample of 472 consecutively referred children and adolescents from a pediatric psychopharmacology clinic.[19] Panic disorder was found in 6% and agoraphobia in 15% of this sample. Thirteen youths (52%) with panic disorder both with and without agoraphobia had comorbid bipolar disorder. Of

those youths with agoraphobia, only 23 (31%) had comorbid bipolar disorder.

Birmaher et al.[20] assessed whether bipolar disorder was specifically associated with panic disorders in youths. Youths (N = 2025) aged 5 to 19 years from a mood and anxiety specialty clinic received a psychiatric assessment. The patients were divided into groups as follows: panic disorder (N = 42), non–panic disorder anxiety disorders (N = 407), and psychiatric controls with no anxiety diagnosis (N = 1576). It was found that youths with panic disorder were more likely to have bipolar disorder (N = 8; 19%) than youths with non–panic disorder anxiety disorders (N = 22; 5.4%) or other psychiatric disorders (N = 112; 7.1%). The group with comorbid panic disorder and bipolar disorder had more psychotic episodes and suicidal ideation than any other patient groups in the sample.

In a community sample of 18 adolescents with bipolar I or II disorder, it was found that 2 (11.1%) of the sample had comorbid panic disorder.[4] In a clinic sample of 43 children with bipolar disorder (I or II), 11 (25.6%) had panic disorder or agoraphobia.[13] Comorbid panic disorder was identified in 13 (12%) of 114 children with mania.[14] Of 45 children with bipolar disorder (I or 11), 12 (26.7%) had panic disorder or agoraphobia.[15] In a sample of preschoolers (N = 44) with bipolar disorder, 2 (5%) had comorbid panic disorder. Of 29 school-aged children with bipolar disorder, 5 (17%) had comorbid panic disorder.[8]

The association between age at onset of bipolar disorder in adults and comorbid disorders was assessed in a sample of 210 adults with early-onset illness (before age 18 years; N = 58) and late-onset illness (after age 40 years; N = 39).[21] It was found that the adults who had an early onset of bipolar disorder had a more severe form of the disorder and greater comorbidity with panic disorder (21%) than those adults with a later age at onset of bipolar disorder (2.6%). In a study of familial bipolar disorder, panic disorder was diagnosed in 18% of family members with bipolar disorder.[22]

In contrast to studies reporting high rates of panic disorder in children with bipolar disorder, Tillman et al.[7] found no cases of comorbid panic disorder in a sample of 93 children and adolescents with bipolar disorder. However, these investigators did report that 7 (7.5%) of the youths had panic attacks.

COMORBID POSTTRAUMATIC STRESS DISORDER

A medical record review was conducted of 83 patients, aged 7 to 20 years, with a diagnosis of bipolar I disorder who received treatment in the public mental health system.[23] Fifteen (18%) of these patients had comorbid posttraumatic stress disorder. Of these patients, 47% had experienced a life threatening or serious injury event and 53% had responded with intense fear or helplessness.

In 44 preschoolers with bipolar I disorder, 6 (14%) had comorbid posttraumatic stress disorder. Among 29 children aged 7 to 9 years with bipolar I disorder, 2 (7%) had comorbid posttraumatic stress disorder.[8]

Ackerman et al.[24] examined the prevalence of posttraumatic stress disorder and other psychiatric diagnoses in 204 abused children. It was found that 9% of these children had a diagnosis of bipolar disorder.

A 4-year longitudinal study of 260 children and adolescents with and without ADHD was conducted to determine the relationship between trauma and ADHD.[25] It was found that youths with ADHD who were exposed to trauma had significantly higher baseline rates of bipolar disorder (27%) than those with ADHD who were not exposed to trauma (9%). Importantly, these investigators found that early bipolar disorder in children with ADHD was the most significant predictor for subsequent trauma. They concluded that early bipolar disorder is an important antecedent for later trauma rather than the consequence of trauma.

COMORBID ANXIETY DISORDERS

As discussed above, youths with bipolar disorder are at increased risk for an anxiety disorder. In the largest study to date, Harpold et al.[26] examined the association between anxiety disorders and bipolar disorder to determine whether there is a significant increased risk for multiple anxiety disorders or whether bipolar disorder is specifically linked to a particular anxiety disorder. The study sample included 297 children and adolescents, aged 8 to 16 years, from a child psychiatry clinic who met diagnostic criteria for bipolar I or II disorder. Since bipolar disorder is often comorbid with disruptive behavior disorders, a group of 1385 youths with disruptive behavior disorders (without bipolar disorder) was used as a comparator.

The mean age at onset of an anxiety disorder in the bipolar disorder group was 4.2 years, which was similar to the mean age at onset (4.4 years) in the disruptive behavior disorders group. The mean duration of illness for an anxiety disorder was similar between the bipolar disorder group and the disruptive behavior disorders group, 5.9 and 5.6 years, respectively.[26]

It was found that youths with bipolar disorder were twice as likely as those with disruptive behavior disorders to have anxiety disorders. In a comparison between youths with bipolar disorder and disruptive behavior disorders, the specific anxiety disorders and odds ratios (ORs) were as follows: posttraumatic stress disorder (OR = 5.4), panic disorder (OR = 3.2), agoraphobia (OR = 2.6), separation anxiety (OR = 2.3), overanxious disorder (OR = 2.2), social phobia (OR = 2.1), and obsessive-compulsive disorder (OR = 2.0). There was no difference in the rates of occurrence of simple phobia between the groups. The results of this study dem-

onstrate that bipolar disorder significantly increased the risk of a wide range of anxiety disorders in youth.[26]

In a clinical sample of 43 outpatient children and adolescents aged 7 to 18 years with bipolar I or II disorder, 41.6% had more than one anxiety disorder.[13] Fifty-three percent of 114 clinically referred children with mania were found to have more than one anxiety disorder.[14]

AGE AT ONSET

The age at onset for anxiety disorders tends to precede the age at onset for bipolar disorder in children. Masi et al.[13] reported that the mean age at onset of bipolar disorder was 12.3 years, whereas the mean age at onset of anxiety disorders ranged from 6.1 years to 10.3 years.

In a sample of children with obsessive-compulsive disorder, the mean age at onset of obsessive-compulsive disorder preceded the mean age at onset of bipolar disorder.[12] Similarly, Masi et al.[11] found that obsessive-compulsive symptoms in children usually preceded the onset of bipolar disorder. These investigators hypothesized that anxiety symptoms are the first internalizing phase in early-onset bipolar disorder.

On the basis of family-genetic findings, Wozniak et al.[27] suggested that comorbid anxiety may be a marker of very–early-onset bipolar disorder. Birmaher et al.[20] found that youths with panic disorder are at higher risk for the development of bipolar disorder and that panic disorder may be a marker of risk for bipolar disorder. Bashir et al.[28] noted that a history of anxiety disorders is often described in adolescents who subsequently develop bipolar disorder.

In a follow-up study of adolescents into adulthood, it was found that adolescents with anxiety disorders were at increased risk for bipolar or clinically significant manic symptoms during early adulthood.[29] Similarly, in a longitudinal follow-up of adolescents with unipolar major depressive disorder, it was found that the onset of anxiety disorders preceded the development of bipolar disorder.[30] It has also been reported that children of parents with bipolar disorder have anxiety symptoms and may initially be diagnosed with an anxiety disorder.[31–33] In contrast to these findings, Tillman et al.[7] reported that the onset of anxiety disorders occurred after the first manic episode in a sample of children with early-onset bipolar disorder.

DIAGNOSTIC AND TREATMENT IMPLICATIONS

Given the substantial comorbidity between pediatric bipolar disorder and anxiety disorders, it is important to carefully evaluate every child who has bipolar disorder for the presence of comorbid anxiety disorders. The pronounced symptoms of bipolar disorder such as severe irritability or rapidly fluctuating mood may mask underlying obsessive thoughts, worries, compulsions, or somatic symptoms associated with anxiety disorders. Parents may describe the behavioral problems associated with bipolar disorder and overlook anxiety symptoms. The clinical interview should include a comprehensive assessment of symptoms related to specific anxiety disorders.

The management of a child with bipolar disorder and comorbid anxiety disorder poses clinical challenges with respect to pharmacologic treatment. Mood stabilization is often the first goal of treatment, since the symptoms of bipolar disorder produce the most functional impairment for the child. Once a child's mood symptoms are adequately treated, the focus of treatment shifts to the anxiety disorder.

Concerns have been raised about the potential for mood destabilization if a child is treated with an antidepressant for a comorbid anxiety disorder. Masi et al.[13] found that pharmacologic hypomania after treatment with an antidepressant occurred more frequently among children with bipolar disorder and comorbid anxiety disorder compared to those without a comorbid anxiety disorder. In their sample, pharmacologic hypomania occurred in 12 (36.4%) of 33 youths with bipolar disorder and comorbid anxiety disorder compared to 0 of 10 cases in youths without anxiety comorbidity. In another study, it was found that pharmacologic hypomania occurred in 9 (30%) of 30 youths with comorbid bipolar disorder and obsessive-compulsive disorder compared to 8 (21.6%) of 37 youths with bipolar disorder only.[11] These investigators commented that high doses of antidepressants are often required in the treatment of obsessive-compulsive symptoms, which may result in the induction of manic symptoms. Birmaher et al.[20] noted that children with panic disorder may also have bipolar disorder and that pharmacologic treatment with an antidepressant has the potential to induce symptoms of mania or hypomania.

Therefore, if a clinician decides to treat the comorbid anxiety disorder with an antidepressant, the child should be carefully monitored for the potential of manic or hypomanic symptoms. To avoid the possibility of mood destabilization, psychotherapeutic approaches, such as cognitive-behavioral therapy, would be a preferable treatment option for the comorbid anxiety disorder.

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

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