Comorbid Anxiety in Children and Adolescents With Bipolar Spectrum Disorders: Prevalence and Clinical Correlates

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Objective: Anxiety disorders are among the most common comorbid conditions in youth with bipolar disorder. We aimed to examine the prevalence and correlates of comorbid anxiety disorders among youth with bipolar disorder.

Method: As part of the Course and Outcome of Bipolar Youth study, 446 youth, ages 7 to 17 years, who met *DSM-IV* criteria for bipolar I disorder (n = 260) or bipolar II disorder (n = 32) or met operationalized criteria for bipolar disorder not otherwise specified (n = 154) were included. Subjects were evaluated for current and lifetime Axis I psychiatric disorders at intake using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime version, and standardized instruments were used to assess functioning and family history.

Results: Forty-four percent (n = 194) of the sample met *DSM-IV* criteria for at least 1 lifetime anxiety disorder, most commonly separation anxiety (24%) and generalized anxiety disorders (16%). Nearly 20% met criteria for 2 or more anxiety disorders. Overall, anxiety disorders predated the onset of bipolar disorder. Subjects with bipolar II disorder were more likely than subjects with bipolar I disorder or bipolar disorder not otherwise specified to have a comorbid anxiety disorder. After adjusting for confounding factors, youth with bipolar disorder with anxiety were more likely to have bipolar II disorder; longer duration of mood symptoms; more severe ratings of depression; and family history of depression, hopelessness, and somatic complaints during their worst lifetime depressive episode than those without anxiety.

Conclusions: Comorbid anxiety disorders are common in youth with bipolar disorder, and they most often predate bipolar disorder onset. Bipolar II disorder, a family history of depression, and more severe lifetime depressive episodes distinguish youth with bipolar disorder with comorbid anxiety disorders from those without. Careful consideration should be given to the assessment of comorbid anxiety in youth with bipolar disorder.

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Onset of bipolar disorder during childhood significantly affects an individual's psychosocial development. Moreover, youth with bipolar disorder are at high risk for suicidal behaviors and completed suicide, substance abuse, and legal problems, and they have particularly high rates of health services utilization.[1–3]

Some of the most common comorbid disorders among youth with bipolar disorder are the anxiety disorders.[4] Since anxiety disorders are also accompanied by significant impairment in the psychosocial functioning of the child,[5] it is important to evaluate the prevalence and clinical correlates of the association between bipolar disorder and anxiety in youth. The few studies that have addressed this issue in small samples of youth with bipolar disorder have shown lifetime prevalence of comorbid anxiety disorders between 14% and 56%, with a weighted average of 27%.[3,6–10] Moreover, family studies have consistently shown high rates of anxiety disorders in offspring of parents with bipolar disorder.[11–15]

The above-noted findings are consistent with the adult epidemiologic[16–18] and clinical literature.[19,20] In fact, retrospective data from studies of adults with bipolar disorder indicate higher rates of comorbid lifetime anxiety disorders among those with earlier age at bipolar disorder onset. Specifically, in 1 study by Perlis and colleagues,[21] adults who reported bipolar disorder onset before age 13 years demonstrated a 70% rate of comorbid lifetime anxiety disorder as compared with 54% of those with bipolar disorder onset between 13 and 18 years and 38% of those with bipolar disorder onset after age 18 years.

Prior research indicates that the presence of comorbid anxiety disorders negatively affects course, outcome, and treatment response in bipolar disorder. In a study by Masi and colleagues,[22] youth with bipolar disorder with panic disorder, as compared to those without panic, demonstrated less bipolar disorder severity at baseline but had poorer response to treatment. Furthermore, DelBello and colleagues[7] found that adolescents with bipolar disorder and comorbid anxiety had more severe mood symptoms and lower rates of recovery 1 year after index hospitalization than adolescents without comorbid anxiety. Similarly, studies among adults with bipolar disorder consistently find that the presence of comorbid anxiety is associated with worse course and outcomes, including higher rates of rapid cycling, more severe depression, substance abuse, and suicide attempts, as well as lower rates of treatment response and recovery. Furthermore,

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adult patients with bipolar disorder and comorbid anxiety report poorer psychosocial functioning and lower overall quality of life.[19,20]

The association between bipolar disorder and comorbid anxiety disorders is of particular clinical significance, since the pharmacologic treatment for anxiety disorders with the most evidence of efficacy in both children and adults is the use of selective serotonin reuptake inhibitors (SSRIs).[23–25] Unfortunately, these medications have been shown to destabilize the symptoms of bipolar disorder.[26,27]

Given the clinical relevance of comorbid anxiety and bipolar disorder and the existence of few studies with small samples, we aimed to investigate the prevalence, correlates, and familial risk associated with comorbid anxiety disorder in a large sample of children and adolescents with bipolar disorder spectrum disorders. We hypothesized that, as compared with youth with bipolar disorder and no comorbid anxiety (BP/no anxiety), those with bipolar disorder and a comorbid anxiety disorder (BP/anxiety) would have (1) earlier bipolar disorder onset and more severe lifetime bipolar disorder symptoms, (2) higher rates of suicidal behavior and substance use disorders, (3) poorer overall functioning, and (4) higher rates of familial mood and anxiety disorders.

METHOD

Subjects and Procedures

The methods for the Course and Outcome of Bipolar Youth (COBY) study have been described in detail elsewhere.[3,28] Briefly, 446 youth, ages 7 to 17 years 11 months (mean = 12.7 years, SD = 3.2 years), who met criteria for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[29] bipolar I disorder (n = 260), bipolar II disorder (n = 32), and operationally defined bipolar disorder not otherwise specified (NOS; n = 154)[3,28,30] were recruited primarily though clinical referrals from 3 academic medical centers (University of Pittsburgh [Pittsburgh, Pennsylvania], Brown University [Providence, Rhode Island], and University of California at Los Angeles [Los Angeles, California]). Institutional review board approval was obtained at each site prior to subject enrollment.

Because the *DSM-IV* criteria for bipolar disorder NOS are vague, the COBY study investigators set the minimum inclusion threshold for the bipolar disorder NOS group as subjects who did not meet the *DSM-IV* criteria for bipolar I disorder or bipolar II disorder but had a distinct period of abnormally elevated, expansive, or irritable mood plus the following: (1) 2 *DSM-IV* manic symptoms (3 if the mood is irritability only) that were clearly associated with the onset of abnormal mood; (2) a clear change in functioning; (3) mood and symptom duration of a minimum of 4 hours within a 24-hour period for a day to be considered meeting the diagnostic threshold; and (4) a minimum of 4 days (not necessarily consecutive) meeting the mood, symptom, duration, and functional change criteria over the subject's lifetime, which could be two 2-day episodes, four 1-day episodes, or another variation.

Children and parents were directly interviewed for the presence of current and lifetime psychiatric disorders using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime version (K-SADS-PL),[30] the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Mania Rating Scale (K-SADS-MRS),[31] and the depression section of the K-SADS-P (from which the Dep-12 depression rating scale was extracted). The K-SADS-PL utilized in COBY did not include the new pervasive developmental disorder (PDD) module. For PDD, we used a *DSM-IV* checklist.

Parents were interviewed at intake about their personal psychiatric history using the Structured Clinical Interview for *DSM-IV* (SCID),[32] and about their first- and second-degree psychiatric family history using the Family History Screen (FHS).[33] The Petersen Pubertal Developmental Scale (PDS)[34] was used to evaluate and categorize pubertal stages. Socioeconomic status was measured using the Hollingshead 4-factor scale (Hollingshead AB, 1975, unpublished), and functional impairment was assessed using the Children's Global Assessment Scale (CGAS).[35]

Research interviewers were trained to high reliability in administration of the K-SADS, the SCID, and the FHS before interviewing any subjects or parents. The results of each interview were reviewed by a child psychiatrist or psychologist. Diagnostic reliability was measured by having research interviewers from all sites rate 13 audiotapes of actual COBY study interviews. There was high reliability for differentiating subjects with bipolar disorder from non–bipolar disorder subjects ($\kappa = 0.90$) and for the bipolar disorder diagnostic subtypes ($\kappa = 0.79$). For the non–mood disorders, κ values were 0.80 or higher. The intraclass correlation coefficient was 0.96 for the K-SADS-MRS and 0.98 for the K-SADS depression scale.

We considered subjects positive for the presence of any lifetime anxiety disorder if they met full threshold criteria for at least 1 of the following disorders: separation anxiety disorder, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), social phobia, panic disorder, anxiety disorder NOS, or agoraphobia. Obsessive-compulsive disorder and PTSD have often been classified as distinct from other anxiety disorders for the complexity of the clinical description and diagnosis. Obsessive-compulsive disorder is characterized by the presence of either obsessions or compulsions, and PTSD refers to a characteristic set of psychological and physiologic symptoms following exposure to a stressor event. The majority of subjects with OCD or PTSD also met criteria for a different anxiety disorder (11.9%), and that is the reason that we decided to include them in the BP/anxiety group—because both cause marked distress and significant impairment similar to the other anxiety disorders. Twenty-nine youth with only specific phobia (eg, fear of spider, dark, or insects) were excluded from the BP/anxiety group because simple phobias are ubiquitous. In addition, they are one of the least reliable anxiety diagnoses in children, perhaps due, in part, to imprecision in standards for distress and

Table 1. Demographic Factors Associated With BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Demographic Factor	BP/ Anxiety (n = 194)	BP/No Anxiety (n = 252)	Statistic	*P* Value
Age, mean ± SD, y	12.8 ± 3.3	12.6 ± 3.2	$t = -0.62$	.5
Sex, male, %	54.6	52.0	$\chi^2 = 0.31$	.6
Race, white, %	81.4	81.4	$\chi^2 = 0.0006$	1.0[a]
Socioeconomic status, mean ± SD	3.3 ± 1.2	3.5 ± 1.2	Kruskal-Wallis = 4.27	.04
Living with both natural parents, %	36.6	45.2	$\chi^2 = 3.37$	.07
Pubertal status, %			$\chi^2 = 2.46$	.3
I	21.4	28.8	$\chi^2 = 2.44$	.1
II–III	29.9	27.8	$\chi^2 = 0.19$	.7
IV–V	48.7	43.5	$\chi^2 = 0.95$	.3

[a]Fisher exact test.
Abbreviations: BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety.

impairment, since the threshold between a fear and a phobia is not always straightforward.[36]

Youth with autism were not included because it is very difficult to obtain information about their mood status, and about 70% have low IQ. Subjects with IQ less than 70 were excluded from the grant. In contrast, youth with Asperger's disorder or PDD NOS were recruited. In COBY, only 2% of the subjects fulfilled criteria for these disorders.

Statistical Analyses

Between-group comparisons in demographic factors were carried out using standard parametric and nonparametric univariate tests. Results were adjusted for bipolar disorder subtype and any other significant between-group demographic differences. Those variables with *P* values ≤ .25 were then entered into a multivariate logistic regression. Exploratory analyses were carried out examining the presence or absence of mood symptoms during the most severe lifetime episodes using the items from the K-SADS-MRS and the Dep-12 plus the hopelessness and aches and pains questions from the K-SADS-P depression section, because these symptoms have been associated with more severe anxiety.[37,38] All *P* values were based on 2-sided tests, and, when appropriate, we used Bonferroni corrections to keep the family-wise error rate at $\alpha = .05$, at most. Odds ratios (ORs) and confidence intervals (CIs) were computed.

RESULTS

Prevalence and Demographics

Forty-four percent (194/446) of subjects met lifetime criteria for at least 1 comorbid anxiety disorder. The most common comorbid anxiety disorders included separation anxiety disorder (n = 108, 24%) and GAD (n = 71, 16%), followed by OCD (n = 29, 7%), PTSD (n = 27, 6%), social phobia (n = 26, 6%), panic disorder (n = 25, 6%), anxiety disorder NOS (n = 11, 3%), and agoraphobia (n = 10, 2%). Eighteen percent of subjects had more than 1 lifetime anxiety disorder, and 5% met criteria for 3 or more anxiety disorders. The proportion of subjects whose age at onset of anxiety was less than age at onset of bipolar disorder was 78.7% (151 out of 192 subjects, as 2 subjects were missing information on age at onset of anxiety). The means and standard deviations of age at onset of anxiety and bipolar disorder for these 192 subjects were 6.3 ± 3.3 years and 9.0 ± 3.7 years, respectively.

Table 2. Frequencies of Bipolar Disorder Subtype Versus Presence of Any Lifetime Anxiety Disorder[a]

Subtype	Anxiety, n (%)	No Anxiety, n (%)
Bipolar I disorder	108/260 (41.5)	152/260 (58.5)
Bipolar II disorder	22/32 (68.8)	10/32 (31.3)
Bipolar disorder not otherwise specified	64/154 (41.6)	90/154 (58.4)

[a]Overall test for independence: $\chi^2_2 = 8.94$, *P* value = .01.

As shown in Table 1, compared to the BP/no anxiety group, those with BP/anxiety had significantly lower socioeconomic status, although the actual difference is minimal (3.3 vs 3.5), and a trend to be less likely to live with both natural parents. There were no other between-group demographic differences.

Clinical Characteristics of Bipolar Illness and Comorbidity

As shown in Table 2, the overall χ^2 comparing bipolar disorder subtypes and presence of any lifetime anxiety disorder was significant ($\chi^2_2 = 8.94$, *P* value = .01). However, the differences were only accounted by the bipolar II disorder subtype.

After adjusting for bipolar disorder subtype, socioeconomic status, and living with both natural parents, the BP/anxiety group had significantly longer duration of mood symptoms and higher depression scores for both current and most severe lifetime episodes compared with the BP/no anxiety group. In addition, the BP/anxiety group was more likely to report that their most recent *DSM* mood episode was of the depressive subtype and less likely to indicate that their index episode was of the manic subtype (all *P* values ≤ .05). Lifetime history of suicidal ideation or attempts was not significantly different between groups. There were no other significant differences in comorbidity or functioning between groups (Table 3).

Family History

In comparison with the BP/no anxiety group, those with BP/anxiety were more likely to endorse a positive first- or second-degree family history of depression and anxiety disorders (all *P* values ≤ .001), and a trend of positive first- or second-degree family history of mania or hypomania (*P* value = .06) (Table 3).

Multivariate Logistic Regression

The BP/anxiety group remained significantly associated with bipolar II disorder (OR = 2.34; 95% CI, 1.02–5.35), longer duration of mood symptoms (OR = 1.11; 95% CI, 1.03–1.19), higher current depression scores in Dep-12 (OR = 1.04; 95% CI, 1.02–1.07), fewer manic episodes

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Table 3. Factors Associated With BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Factor	BP/Anxiety (n = 194)	BP/No Anxiety (n = 252)	Wald χ^2 Statistic[a]	*P* Value
Characteristic of bipolar illness, mean ± SD				
Age at onset of mood symptoms, y	7.9 ± 3.9	8.6 ± 4.1	2.54	.1
Age at onset of bipolar disorder episode,[b] y	9.0 ± 3.7	9.6 ± 4.0	1.99	.2
Duration of mood symptoms,[c] y	5.0 ± 3.2	4.0 ± 2.6	9.04	.003
K-SADS-MRS current	22.8 ± 12.2	22.5 ± 12.1	0.0001	1.0[d]
K-SADS-MRS most severe lifetime	34.4 ± 8.5	33.4 ± 8.2	3.0964	.08
Dep-12 current	17.7 ± 10.1	12.4 ± 9.6	25.61	< .0001
Dep-12 most severe lifetime	25.9 ± 10.2	20.4 ± 11.0	17.96	< .0001
CGAS current	55.4 ± 10.8	54.3 ± 13.2	0.54	.5
CGAS most severe lifetime	37.0 ± 11.0	37.9 ± 9.9	1.67	.2
Polarity of index episode, %				
Depressed	20.6	10.3	8.30	.004
Hypomanic	8.8	7.9	0.39	.5
Manic	9.3	25.4	16.69	< .0001
Mixed	19.6	15.1	2.61	.1
Not otherwise specified	41.8	41.3	0.03	.9
Lifetime history of comorbid disorders, % yes				
ADHD	60.8	59.5	0.0002	1.0[d]
ODD	35.1	42.9	2.4019	.1
Conduct disorder	11.3	13.5	1.2377	.3
PDD	0.5	0.0	0.0003	1.0[d]
Substance abuse or dependence	7.2	8.7	0.4081	.5
Alcohol abuse or dependence	3.1	5.6	1.7079	.2
Lifetime phenomenological features and treatment history, % yes				
Psychosis	23.7	19.4	1.4600	.2
Suicide ideation	78.9	73.0	1.0539	.3
Suicide attempts	33.5	27.4	1.5581	.2
Psychiatric hospitalization	54.1	49.8	1.0294	.3
First- or second-degree family history, % subjects				
With depression	94.5	80.9	13.91	.0002
With mania or hypomania	61.1	49.8	3.52	.06
With anxiety	77.7	61.6	10.96	.0009

[a]Logistic regression adjusting for socioeconomic status, living with both natural parents, and bipolar disorder subtype. [b]Age 4 years is set as the minimum value. [c]Since age at onset of any *Diagnostic and Statistical Manual of Mental Disorders* mood episode. [d]Fisher exact test.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety, CGAS = Children's Global Assessment Scale, DEP-12 = depression rating scale extracted from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present version, K-SADS-MRS = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Mania Rating Scale, ODD = oppositional defiant disorder, PDD = pervasive developmental disorder (pervasive developmental disorder NOS or Asperger's disorder).

(OR = 0.38; 95% CI, 0.2–0.73), and higher rates of depression among first- or second-degree relatives (OR = 3.58; 95% CI, 1.62–7.93) (Table 4).

Severity of Manic and Depressive Symptoms

We examined whether there were differences between the BP/anxiety and BP/no anxiety groups in the severity of manic and depressive symptoms. Exploratory analyses, adjusted for multiple comparisons, were conducted using ratings from the most severe lifetime manic or hypomanic (K-SADS-MRS) and depressive episodes (Dep-12). Only symptoms rated at mild or higher (≥ 3) were analyzed. There were no between-group differences in manic or hypomanic symptoms. In contrast, youth with BP/anxiety depressive episodes had significantly more depressed mood, hopelessness, aches and pains, anhedonia, and fatigue after controlling for multiple comparisons using Bonferroni correction. Suicidal ideation was also significantly higher in the BP/anxiety group but did not survive Bonferroni correction (Table 5).

In the multivariate analysis of Dep-12, hopelessness (OR = 2.1; 95% CI, 1.28–3.28) and aches and pains (OR = 2.5; 95% CI, 1.56–3.95) were the only 2 items that were significant in the BP/anxiety group during their worst lifetime depressive episode.

DISCUSSION

To our knowledge, this is the largest study to date examining prevalence and demographic and clinical correlates of comorbid anxiety disorder among children and adolescents with bipolar disorder.

Forty-four percent of youth with bipolar disorder in our sample met criteria for at least 1 lifetime anxiety disorder, most commonly separation anxiety disorder and GAD; 18% had 2 or more lifetime anxiety disorders. On average, the onset of anxiety predated the onset of bipolar disorder. After adjusting for significant demographic factors and bipolar disorder subtypes, youth with BP/anxiety, as compared with BP/no anxiety, showed significantly higher rates of bipolar II disorder, longer duration of mood symptoms, higher current depression scores, lower likelihood of reporting an index episode of the manic subtype, and higher rates of familial depression, and they had a worst lifetime depressive episode characterized by greater severity of hopelessness and aches and pains.

Our findings are consistent with those of previous studies in which anxiety disorders, particularly separation anxiety disorder and GAD, have been reported at high rates among youth and adults with bipolar disorder.[6,8–10,18,39–45] Also similar to other studies in the child and adult literature, we found that subjects with bipolar disorder with comorbid anxiety disorders were more likely to have a diagnosis of bipolar II disorder,[22,42,44,46–48] longer duration of mood symptoms, and greater severity of depressive episodes.[49–53] This association may be related to the fact that bipolar II disorder has a more chronic course and outcome, longer length of illness, shorter cycles, greater number of episodes, more major and minor depressive episodes, shorter well intervals between episodes, and lower rates of recovery.[54,55] Moreover, we found, similar to the bipolar disorder[9,56] and unipolar depression[57,58] literature, that, on average, the anxiety disorders preceded the onset of the mood disorder. Contrary to our initial hypothesis,[10,40,59–60] age at onset of bipolar disorder episode did not differ between the 2 groups.

Table 4. Logistic Regression of the Variables Associated With BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Variable	OR	95% CI	Wald χ^2 Statistic	*P* Value
Socioeconomic status	0.89	0.74–1.07	1.67	.2
Bipolar II disorder	2.34	1.02–5.35	4.03	.04
Duration of mood symptoms	1.11	1.03–1.19	6.97	.008
Dep-12 current	1.04	1.02–1.07	14.78	.0001
Manic polarity	0.38	0.2–0.73	8.51	.004
First- or second-degree relative with depression	3.58	1.62–7.93	9.91	.002

Abbreviations: BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety, DEP-12 = depression rating scale extracted from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present version.

Table 5. Depressive Symptoms[a] During the Most Severe Lifetime in BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Symptom	BP/Anxiety (n = 194), %	BP/No Anxiety (n = 252), %	Wald χ^2 Statistic	*P* Value
Depressed mood	94.7	81.0	14.28	< .001*
Excessive or inappropriate guilt	53.7	43.8	3.41	.07
Hopelessness	69.5	49.5	14.43	< .001*
Aches and pain	67.3	41.9	22.69	< .001*
Anhedonia	80.0	63.2	11.84	.001*
Fatigue	78.7	61.9	11.471	.001*
Difficulty concentrating	79.5	68.6	5.31	.02
Psychomotor agitation	51.3	49.5	0.115	.7
Psychomotor retardation	55.3	46.7	2.63	.1
Insomnia	74.1	61.0	6.31	.01
Hypersomnia	49.3	38.6	4.13	.04
Anorexia	38.5	33.3	1.01	.3
Increased appetite	32.7	19.6	7.92	.005
Suicidal ideation	65.8	54.8	4.33	.04

[a]Items from the depression rating scale extracted from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present version (Dep-12) plus hopelessness and aches and pain.
*Remained significant after Bonferroni correction.
Abbreviations: BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety.

These findings are clinically relevant because, currently, the first-line pharmacologic treatments for anxiety disorders in youth are the SSRIs.[24,25] Selective serotonin reuptake inhibitors have been shown to trigger or destabilize bipolar disorder symptoms.[26] Thus, it is critically important to evaluate a child presenting with anxiety for the presence of manic or hypomanic symptoms, especially if depressive symptoms and a positive family history of mood disorders are also present. Although hypomanic symptoms can be difficult to ascertain in youth due to the unique developmental presentation[61] as well as symptom overlap with other conditions including depression and anxiety, recent studies clearly demonstrate that mania or hypomania in youth can be reliably diagnosed.[3] Additionally, anxious children treated with antidepressants should be carefully monitored for the presence of manic or hypomanic symptoms.[40]

Little is known about the most efficacious treatments for the treatment of comorbid anxiety in youth with bipolar disorder. Future studies may evaluate the efficacy of psychotherapy approaches with empirical support for the treatment of anxious youth, such as cognitive-behavioral therapy.[23] The risk/benefit ratio of the use of SSRIs in youth with bipolar disorder who are taking concurrent mood stabilizers may also be explored.

Interestingly, we found that youth with BP/anxiety showed significantly more family history of depression. This finding is consistent with Wozniak et al,[62] who reported elevated risk for both bipolar disorder and anxiety among relatives of BP/anxiety probands. As such, this group suggested that comorbid anxiety and bipolar disorder may represent a genetic subtype of bipolar disorder. Furthermore, a recent study by Birmaher and colleagues[11] found that offspring of parents with bipolar disorder had higher rates of anxiety disorders than offspring of control parents, suggesting that anxiety may be a precursor of bipolar disorder among bipolar disorder offspring. Thus, systematic evaluation of youth with anxiety disorder and family history of mood disorders is warranted because these youth may be at high risk to develop bipolar disorder.

Contrary to our initial hypothesis,[4,20,49,59,63–66] we did not find significantly more suicidal behaviors[9] or substance use disorders in the bipolar disorder with comorbid anxiety group as compared to those without. These discrepancies may be explained by the fact that most subjects in this study have not yet reached the age of highest risk for these conditions. Nonetheless, youth with bipolar disorder and anxiety had significantly more suicidal ideation as well as hopelessness during the most severe lifetime depressive episode than subjects without comorbid anxiety. Since hopelessness is highly associated with suicide attempts and suicide,[67–69] careful evaluation and monitoring of suicide risk in youth with BP/anxiety are clearly indicated. Also contrary to our initial hypothesis,[4,20] we did not find poorer functioning in the bipolar disorder group with comorbid anxiety as compared with those without. It is possible that the impact of bipolar disorder on global functioning during childhood and adolescence is significantly profound, such that any additional impairment associated with comorbid anxiety is relatively negligible.

Finally, after adjusting for multiple comparisons, youth with bipolar disorder and comorbid anxiety reported more aches and pains than those without anxiety, as is the case in adult studies.[70] It has been well documented that anxious youth experience somatic complaints and tend to consult primary care physicians or pediatricians before mental health clinicians.[71] Thus, it is important to educate such front-line providers about the possibility that anxious youth with a positive family history of mood disorder may also have bipolar disorder.

It is important to note the limitations of this study. First, as most subjects were white and were recruited primarily from outpatient clinical settings, the generalizability of the findings remains uncertain. However, a community-based

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study of nonreferred adolescents with bipolar disorder reported similarly high rates of comorbid anxiety disorders.[72] Second, subjects were ascertained for bipolarity. Thus, results may not apply to subjects whose primary diagnosis is anxiety and then develop bipolar disorder. Third, this study is cross-sectional, and data were ascertained retrospectively. We are currently following these subjects longitudinally, and we will thus be able to further examine the associations over follow-up. Finally, no psychiatric control group was included. Thus, using the current sample, we cannot conclude that lifetime anxiety disorders are more common in youth with bipolar disorder than in youth with other childhood psychiatric disorders (eg, major depressive disorder).

In summary, anxiety disorders usually predate the onset of bipolar disorder and are very common in youth with bipolar disorder, especially those with bipolar II disorder, longer duration of mood symptoms, more severe depressions, and family history of depression. Given the clinical and treatment implications of these findings, early identification and accurate diagnosis for these youth is very important. Randomized trials to evaluate treatments for anxiety in youth with bipolar disorder are needed. Finally, longitudinal studies to determine the impact of comorbid anxiety disorder on the course and outcome of pediatric bipolar disorder spectrum disorders are warranted.

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