Published in final edited form as:
J Clin Psychiatry. 2010 October ; 71(10): 1344–1350. doi:10.4088/JCP.09m05845gre.

COMORBID ANXIETY IN CHILDREN AND ADOLESCENTS WITH BIPOLAR SPECTRUM DISORDERS: PREVALENCE AND CLINICAL CORRELATES

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Abstract

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

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

Results—Forty-four percent (n=194) of the sample met DSM-IV criteria for at least one lifetime anxiety disorder, most commonly Separation Anxiety (24%) and Generalized Anxiety Disorders (16%). Nearly 20% met criteria for two or more anxiety disorders. Overall, anxiety disorders predated the onset of BP. BP-II subjects were more likely than BP-I or BP-NOS subjects to have a comorbid anxiety disorder. After adjusting for confounding factors, BP youth with anxiety were more likely

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The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

Preliminary findings were presented in poster form at the 56th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 2009, Hawai'i, HI, USA.

to have BP-II, 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 BP, and most often predate BP onset. BP-II, a family history of depression, and more severe lifetime depressive episodes distinguish BP youth with comorbid anxiety disorders from those without. Careful consideration should be given to the assessment of comorbid anxiety in BP youth.

Keywords

Youth; anxiety; bipolar disorder; prevalence; clinical correlates

INTRODUCTION

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

Some of the most common comorbid disorders among youth with BP 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 BP and anxiety in youth. The few studies that have addressed this issue in small samples of youth with BP, 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 BP [11–15].

The above-noted findings are consistent with the adult epidemiological [16–18] and clinical literature [20–23]. In fact, retrospective data from studies of adults with BP indicate higher rates of comorbid lifetime anxiety disorders among those with earlier age of BP onset. Specifically, in one study by Perlis and colleagues (2004), adults who reported BP onset before age 13 demonstrated a 70% rate of comorbid lifetime anxiety disorder, as compared with 54% of those with BP onset between 13 and 18 years, and 38% of those with BP onset after age 18 [24].

Prior research indicates that the presence of comorbid anxiety disorders negatively affects course, outcome, and treatment response in BP. In a study by Masi and colleagues (2007), BP youth with panic disorder, as compared to those without panic, demonstrated less BP severity at baseline, but had poorer response to treatment [19]. Furthermore, DelBello and colleagues (2007) found that adolescents with BP and comorbid anxiety had more severe mood symptoms and lower rates of recovery one year after index hospitalization than adolescents without comorbid anxiety [7]. Similarly, studies among adults with BP consistently find 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, adult patients with BP and comorbid anxiety report poorer psychosocial functioning and lower overall quality of life [20, 21].

The association between BP and comorbid anxiety disorders is of particular clinical significance since the pharmacological treatment for anxiety disorders with the most evidence of efficacy in both children and adults is the serotonin reuptake inhibitors (SSRIs) [22–24]. Unfortunately, these medications have been shown to destabilize the symptoms of BP [25, 26].

Given the clinical relevance of comorbid anxiety and BP 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 BP spectrum disorders. We hypothesized that as compared with youth with BP and no comorbid anxiety (BP/no-anxiety), those with BP and a comorbid anxiety disorder (BP/anxiety) would have: (1) earlier BP onset and more severe lifetime BP 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.

METHODS

Subjects and procedures

The methods for the Course and Outcome of Bipolar Youth (COBY) study have been described in detail elsewhere [3, 27]. Briefly, 446 youth, ages 7 to 17 years 11 months (mean = 12.7, SD = 3.2) who met criteria for Diagnostic and Statistical Manual IV (DSM-IV) [28] BP-I (n=260), BP-II (n=32), and operationally defined BP-NOS (n=154) [3, 27, 29] were recruited primarily though clinical referrals from three academic medical centers (University of Pittsburgh, Brown University, and University of California at Los Angeles). Institutional Review Board approval was obtained at each site prior to subject enrollment.

Because the *DSM-IV* criteriafor BP-NOS are vague, the COBY study investigators set the minimuminclusion threshold for the BP-NOS group as subjects who did not meet the *DSM-IV* criteria for BP-I or BP-II but had a distinctperiod 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 Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL) [29], the Kiddie Mania Rating Scale (K-MRS) [30], and the depression section of the KSADS-P (from which the Dep-12 depression rating scale was extracted). The KSADS-PL utilized in COBY did not include the new 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 (SCID) [31] for DSM-IV, and about their first- and second-degree psychiatric family history using the Family History Screen (FHS) [32]. The Petersen Pubertal Developmental Scale (PDS) [33] was used to evaluate and categorize pubertal stages. Socioeconomic status was measured using the Hollingshead four-factor scale [34], and functional impairment was assessed using the Child Global Assessment Scale (CGAS) [35].

Research interviewers were trained to high reliability in administration of the KSADS, the Structured Clinical Interview for *DSM-IV*, and the Family History Screen 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 BP from non-BP subjects (κ= 0.90)and for the BP diagnostic subtypes κ= 0.79). For the non mood disorders, κvalues were 0.80 or higher. The intraclass correlation coefficient was 0.96 for the KSADS MRS and 0.98 for the KSADS Depression Scale.

We considered a subject positive for the presence of any lifetime anxiety disorder if they met full threshold criteria for at least one of the following disorders: Separation Anxiety Disorder (SAD), Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), Post-traumatic Stress Disorder (PTSD), Social Phobia, Panic Disorder, Anxiety Disorder Not Otherwise Specified (Anxiety NOS), or Agoraphobia. OCD and PTSD have been often classified as distinct from other anxiety disorders for the complexity of the clinical description and diagnosis. OCD 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%) 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 others anxiety disorders. Twenty-nine youth with only specific phobia (i.e. fear to spider, dark, and 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 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 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 BP subtype and any other significant between group demographic differences. Those variables with p-values ≤ 0.25 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-MRS, and the Dep-12 plus the Hopelessness and Aches and Pains questions from the KSADS-P depression section, because these symptoms have been associated with more severe anxiety [37, 38]. All p-values are based on two-sided tests; when appropriate, we use Bonferroni corrections to keep the family-wise error rate at most alpha=0.05. Odds ratios (OR) and confidence intervals (CI) were computed.

RESULTS

Prevalence and demographics

Forty-four percent (194/446) of subjects met lifetime criteria for at least one comorbid anxiety disorder. The most common comorbid anxiety disorders included SAD (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 one lifetime anxiety disorder, and 5% met criteria for three or more anxiety disorders. The proportion of subjects whose age onset of anxiety is less than age onset of BP was 78.7% (151 out of 192 subjects as two subjects were missing information of age onset of anxiety). The mean and standard deviation of age onset of anxiety and BP for these 192 subjects were 6.3 ± 3.3 and 9.0 ± 3.7 years, respectively.

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 chi square comparing BP subtypes and presence of any lifetime anxiety disorder was significant (χ^2= 8.94, p-value = 0.01). However the differences were only accounted by the BP-II subtype.

After adjusting for BP subtype, SES, 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/non-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 ≤ 0.05). 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, anxiety disorders (all p-values ≤ 0.001), and a trend of positive first-or-second degree family history of mania/hypomania (p-value =0.06) (Table 3).

Multivariate logistic regression

The BP/anxiety group remained significantly associated with BP-II (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 (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 versus 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/hypomanic (K-MRS) and depressive episodes (Dep-12). Only symptoms rated at mild or higher (≥3) were analyzed. There were no between-group differences in manic/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 two 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, demographic and clinical correlates of comorbid anxiety disorder among children and adolescents with BP.

Forty-four percent of BP youth in our sample met criteria for at least one lifetime anxiety disorder, most commonly SAD and GAD; 18% had two or more lifetime anxiety disorders. On average, the onset of anxiety predated the onset of BP. After adjusting for significant demographic factors and BP subtypes, youth with BP/anxiety, as compared with BP/no-anxiety, showed significantly higher rates of BP-II, longer duration of mood symptoms, higher

current depression scores, lower likelihood of reporting an index episode of the manic subtype, higher rates of familial depression, and 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 SAD and GAD, have been reported at high rates among youth and adults with BP [6, 8–10, 18, 39–45]. Also similar to other studies in the child and adult literature, we found that BP subjects with comorbid anxiety disorders were more likely to have a diagnosis of BP-II [19, 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 BP-II has a more chronic course and outcome, longer length of illness, shorter cycles, and greater number of episodes, more major and minor depressive episodes, shorter well intervals between episodes, and lower rates of recovery [54, 55].

Moreover, similar to the BP [9, 56] and unipolar depression [57, 58] literature we found that, on average, the anxiety disorders preceded the onset of the mood disorder. Contrary to our initial hypothesis [10, 40, 59–61], age onset of BP episode did not differ between the two groups.

These findings are clinically relevant because currently the first line pharmacological treatments for anxiety disorders in youth are the selective serotonin reuptake inhibitors (SSRIs) [23, 24]. SSRIs have been shown to trigger or destabilize BP symptoms [25]. 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 [62] as well as symptom overlap with other conditions including depression and anxiety, recent studies clearly demonstrate that mania/hypomania in youth can be reliably diagnosed [3]. Additionally, anxious children treated with antidepressants should be carefully monitored for the presence of manic/hypomanic symptoms [40].

Little is known about the most efficacious treatments for the treatment of comorbid anxiety in youth with BP. Future studies may evaluate the efficacy of psychotherapy approaches with empirical support for the treatment of anxious youth, such as cognitive-behavioral therapy [22]. The risk/benefit ratio of the use of SSRIs in youth with BP who are on concurrent mood stabilizers also may 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. (2002) [63], who reported elevated risk for both BP and anxiety among relatives of BP/anxiety probands. As such, this group suggested that comorbid anxiety and BP may represent a genetic subtype of BP. Furthermore, a recent study by Birmaher and colleagues (2009) [11] found that offspring of parents with BP had higher rates of anxiety disorders than offspring of control parents suggesting that anxiety may be a precursor of BP among BP 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 BP.

Contrary to our initial hypothesis [4, 21, 49, 59, 64–67], we did not find significantly more suicidal behaviors [9], or substance use disorders in the BP 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 BP 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 [68–70], careful evaluation and monitoring of suicide risk in youth with BP/anxiety is clearly indicated. Also contrary to our initial hypothesis [4, 21], we did not find poorer functioning in the BP group with comorbid anxiety as

compared with those without. It is possible that the impact of BP 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 BP and comorbid anxiety reported more aches and pains than those without anxiety, as is the case in adults studies [71]. It has been well-documented that anxious youth experience somatic complaints and tend to consult primary care physicians or pediatricians before mental health clinicians [72]. 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 BP.

It is important to note the limitations of this study. First, as most subjects were Caucasian and were recruited primarily from outpatient clinical settings, the generalizability of the findings remains uncertain. However, a community-based study of non-referred adolescents with BP reported similarly high rates of comorbid anxiety disorders [73]. Second, subjects were ascertained for bipolarity. Thus, results may not apply to subjects whose primary diagnosis is anxiety and then develop BP. Third, this study is cross-sectional and data was 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 BP than in youth with other childhood psychiatric disorders (e.g., major depressive disorder).

In summary, anxiety disorders usually predate the onset of BP and are very common in youth with BP, especially those with BP-II, 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 BP are needed. Finally, longitudinal studies to determine the impact of comorbid anxiety disorder on the course and outcome of pediatric BP spectrum disorders are warranted.

Acknowledgments

Dr. Sala was supported by a grant from the Alicia Koplowitz Foundation. Funding for this study was provided by National Institute of Mental Health Grants MH59929 (Dr. Birmaher), MH59977 (Dr. Strober), and MH59691 (Dr. Keller). The NIMH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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Table 1

Demographic factors associated with BP/anxiety vs. BP/non-anxiety in children and adolescent with bipolar disorder spectrum

	BP/anxiety (n=194)	BP/non-anxiety (n=252)	Statistics	p-value
Demographic Factors				
Age	12.8 ± 3.3	12.6 ± 3.2	t=−0.62	0.5
Sex (Male) (%)	54.6	52.0	X^2=0.31	0.6
Race (White) (%)	81.4	81.4	X^2=0.0006	1.0
Socioeconomic Status	3.3 ± 1.2	3.5 ± 1.2	K-W=4.27	0.04
Living with both natural parents (%)	36.6	45.2	X^2=3.37	0.07
Pubertal Status (%)			X^2=2.46	0.3
I	21.4	28.8	X^2=2.44	0.1
II–III	29.9	27.8	X^2=0.19	0.7
IV–V	48.7	43.5	X^2=0.95	0.3

Table 2

Frequencies of BP subtype vs. presence of any lifetime anxiety disorder

BP subtype	Anxiety	No-anxiety
BP-I (%)	108/260 (41.5)	152/260 (58.5)
BP-II (%)	22/32 (68.8)	10/32 (31.3)
BP-NOS (%)	64/154 (41.6)	90/154 (58.4)

Overall test for independence: $\chi^2_{df=2} = 8.94$, p-value = 0.01

Table 3

Factors associated with BP/anxiety vs. BP/non-anxiety in children and adolescent with bipolar disorder spectrum

	BP/anxiety (n=194)	BP/non-anxiety (n=252)	Wald chi-sq. statistic [a]	p-value
Characteristics of Bipolar Illness				
Age onset of mood Symptoms	7.9 ± 3.9	8.6 ± 4.1	2.54	0.1
Age onset BP episode*	9.0 ± 3.7	9.6 ± 4.0	1.99	0.2
Duration of mood symptoms **	5.0 ± 3.2	4.0 ± 2.6	9.04	0.003
MRS Current	22.8 ± 12.2	22.5 ± 12.1	0.0001	1.0
MRS Most Severe Lifetime	34.4 ± 8.5	33.4 ± 8.2	3.0964	0.08
Dep-12 -current	17.7 ± 10.1	12.4 ± 9.6	25.61	<.0001
Dep-12 -MSL	25.9 ± 10.2	20.4 ± 11.0	17.96	<.0001
CGAS -current	55.4 ± 10.8	54.3 ± 13.2	0.54	0.5
CGAS-MSL	37.0 ± 11.0	37.9 ± 9.9	1.67	0.2
Polarity of Index Episode (%)				
Depressed	20.6	10.3	8.30	0.004
Hypomanic	8.8	7.9	0.39	0.5
Manic	9.3	25.4	16.69	<.0001
Mixed	19.6	15.1	2.61	0.1
NOS	41.8	41.3	0.03	0.9
Lifetime History of Comorbid Disorders (%Yes)				
ADHD	60.8	59.5	0.0002	1.0
ODD	35.1	42.9	2.4019	0.1
Conduct Disorder	11.3	13.5	1.2377	0.3
PDD	0.5	0	0.0003	1.0
Substance abuse/dependence	7.2	8.7	0.4081	0.5
Alcohol abuse/dependence	3.1	5.6	1.7079	0.2
Lifetime Phenomenological Features and Treatment History (% Yes)				
Psychosis	23.7	19.4	1.4600	0.2
Suicide Ideation	78.9	73.0	1.0539	0.3
Suicide Attempts	33.5	27.4	1.5581	0.2
Psychiatric Hospitalization	54.1	49.8	1.0294	0.3
Family History: % subjects				
1st or 2nd degree with depression	94.5	80.9	13.91	0.0002
1st or 2nd degree with mania/hypomania	61.1	49.8	3.52	0.06
1st or 2nd degree with anxiety	77.7	61.6	10.96	0.0009

SES: socioeconomic status; BP: Bipolar Disorder; BP-I: Bipolar I Disorder; BP-II: Bipolar II Disorder; BP-NOS: Bipolar Not-Otherwise-Specified; MRS: Mania Rating Scale; CGAS: Child Global Assessment Scale; ADHD: Attention-Deficit/Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; PDD: Pervasive Developmental Disorder (Pervasive Developmental Disorder NOS or Asperger Disorder); K-W: Kruskal-Wallis; FET: Fisher Exact Test.

*Age 4 is set as the minimum value.

** Since age of onset of any DSM mood episode.

[a] Logistic regression adjusting SES, living with both natural parents and BP subtype

Table 4

Logistic regression of the variables associated with BP/anxiety vs. BP/no-anxiety in children and adolescents with bipolar disorder spectrum

Variable	OR	95%CI	Wald	p
SES	0.89	0.74–1.07	1.67	0.2
BP-II	2.34	1.02–5.35	4.03	0.04
Duration of mood symptoms	1.11	1.03–1.19	6.97	0.008
Dep-12 current	1.04	1.02–1.07	14.78	0.0001
Manic polarity	0.38	0.2–0.73	8.51	0.004
1st or 2nd degree relative with depression	3.58	1.62–7.93	9.91	0.002

SES: socioeconomic status; BP-II: Bipolar II Disorder; MSL: most severe lifetime

Table 5

Depressive symptoms* during the most severe lifetime in BP/anxiety vs. BP/non-anxiety in children and adolescent with bipolar disorder spectrum

	BP/anxiety (%) (n=194)	BP/non-anxiety (%) (n=252)	Statistics	p-value
Depressed mood	94.7	81	X^2=14.28	<0.001**
Excessive or inappropriate guilt	53.7	43.8	X^2=3.41	0.07
Hopelessness	69.5	49.5	X^2=14.43	<0.001**
Aches and pain	67.3	41.9	X^2=22.69	<0.001**
Anhedonia	80	63.2	X^2=11.84	0.001**
Fatigue	78.7	61.9	X^2=11.471	0.001**
Difficulty concentrating	79.5	68.6	X^2=5.31	0.02
Psychomotor agitation	51.3	49.5	X^2=0.115	0.7
Psychomotor retardation	55.3	46.7	X^2=2.63	0.1
Insomnia	74.1	61	X^2=6.31	0.01
Hypersomnia	49.3	38.6	X^2=4.13	0.04
Anorexia	38.5	33.3	X^2=1.01	0.3
Increased appetite	32.7	19.6	X^2=7.92	0.005
Suicidal ideation	65.8	54.8	X^2=4.33	0.04

* Items from Depression Rating Scale (Dep-12) plus hopelessness and aches and pain

** Remained significant after Bonferroni correction