Factors Associated With the Persistence and Onset of New Anxiety Disorders in Youth With Bipolar Spectrum Disorders

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ABSTRACT

Objective: Anxiety disorders are among the most common comorbid conditions in youth with bipolar disorder, but, to our knowledge, no studies examined the course of anxiety disorders in youth and adults with bipolar disorder.

Method: As part of the Course and Outcome of Bipolar Youth study, 413 youth, ages 7 to 17 years who met criteria for *Diagnostic and Statistical Manual*, Fourth Edition *(DSM-IV)* bipolar I disorder (n = 244), bipolar II disorder (n = 28), and operationally defined bipolar disorder not otherwise specified (n = 141) were recruited primarily from outpatient clinics. Subjects were followed on average for 5 years using the Longitudinal Interval Follow-Up Evaluation. We examined factors associated with the persistence (> 50% of the follow-up time) and onset of new anxiety disorders in youth with bipolar disorder.

Results: Of the 170 youth who had anxiety at intake, 80.6% had an anxiety disorder at any time during the follow-up. Most of the anxiety disorders during the follow-up were of the same type as those present at intake. About 50% of the youth had persistent anxiety, particularly generalized anxiety disorder (GAD). Persistence was associated with multiple anxiety disorders, less follow-up time in euthymia, less conduct disorder, and less treatment with antimanic and antidepressant medications (all *P* values ≤ .05). Twenty-five percent of the sample who did not have an anxiety disorder at intake developed new anxiety disorders during follow-up, most commonly GAD. The onset of new anxiety disorders was significantly associated with being female, lower socioeconomic status, presence of attention-deficit/hyperactivity disorder and substance use disorder, and more follow-up time with manic or hypomanic symptoms (all *P* values ≤ .05)

Conclusions: Anxiety disorders in youth with bipolar disorder tend to persist, and new-onset anxiety disorders developed in a substantial proportion of the sample. Early identification of factors associated with the persistence and onset of new anxiety disorders may enable the development of strategies for treatment and prevention.

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Youth with bipolar disorder are among the most psychosocially impaired of psychiatrically ill youth, and the presence of comorbidity compounds disability, complicates treatment, and appears to worsen the prognosis of bipolar disorder.[1] Comorbid conditions frequently associated with pediatric bipolar disorder include attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorders, substance use disorders, anxiety disorders, and pervasive developmental disorders.[2] However, the presence of anxiety disorders in patients who suffer from bipolar disorder has been underrecognized and understudied.[1]

Clinical and epidemiologic studies have documented high rates of comorbid anxiety disorders in youth with bipolar disorder.[3–5] The existent longitudinal studies of comorbid anxiety in youth[6,7] and adults with bipolar disorder[8–11] have shown that anxiety disorders are associated with greater severity of bipolar disorder. For example, Masi and colleagues[6] followed a group of 224 children and adolescents with bipolar disorder spectrum disorder for at least 6 months. They reported that, compared to bipolar disorder youth without panic disorder, those with panic disorder showed less mood improvement during the follow-up. In addition, DelBello and colleagues[7] followed a group of 71 adolescents with bipolar I disorder 1 year after discharge from the hospital. They found that adolescents with bipolar disorder and comorbid anxiety disorder had more severe mood symptoms and lower rates of recovery than adolescents without anxiety.

Studies in adults with bipolar disorder have also found that the presence of comorbid anxiety is associated with shorter euthymic periods, higher depression severity, rapid cycling, longer time to remission from the index episode, increased risk for recurrence, more time with depressive mood, suicidal behavior, substance abuse, lower quality of life, diminished role functioning, and poor response to treatment.[8–14]

The above-noted studies focused on the effect of anxiety on the course of bipolar disorder, but, to our knowledge, there are no studies examining the course of anxiety disorders in youth and adults with bipolar disorder. It is important to examine the course and factors associated with anxiety disorders in youth with bipolar disorder because the early identification and management of the anxiety may improve the prognosis of bipolar disorder.

In a prior publication,[3] as part of the Course and Outcome of Bipolar Youth study, we analyzed the presence of lifetime anxiety disorders in a large group of youth with bipolar disorder. Forty-four percent (194/446) of youth with bipolar disorder met *DSM-IV* criteria for at least 1 lifetime anxiety disorder (mainly separation anxiety disorders and generalized anxiety disorders [GAD]), and 18% met criteria for 2 or more anxiety disorders. The main goal of the current study was to evaluate the longitudinal course of the anxiety disorders of the bipolar disorder youth who had anxiety disorders at intake. More specifically, we sought to evaluate whether the anxiety disorders present during the follow-up were the

same as those present at intake (homotypic continuity) and to identify the intake and follow-up factors associated with the persistence of anxiety disorders. In addition, we evaluated the factors at intake and follow-up that were associated with the development of new anxiety disorders during the follow-up period in youth without any anxiety disorders at intake.

- Anxiety disorders in youth with bipolar disorder tended to persist, and a substantial proportion of subjects developed new anxiety disorders.
- Different factors, including the presence of severe or multiple anxiety disorders, ongoing mood symptoms, and comorbid disorders, were associated with the persistence and the onset of anxiety disorders. Early identification of factors may enable the development of strategies for treatment and prevention of anxiety disorders in bipolar youth.
- Randomized controlled trials are warranted to evaluate the efficacy and tolerability of pharmacologic and psychosocial treatments for youth with comorbid bipolar disorder and anxiety disorders.

Clinical Points

METHOD

Subjects

The sample included in this article consists of 413 youth, ages 7 to 17 years 11 months (mean ± SD, 12.6 ± 3.3 years) who met criteria for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) bipolar I disorder (n = 244), bipolar II disorder (n = 28), and operationally defined bipolar disorder not otherwise specified (NOS) (n = 141) and who had at least 1 follow-up assessment. The sample was recruited primarily though clinical referrals from 3 academic medical centers (University of Pittsburgh [Pennsylvania], Brown University [Providence, Rhode Island], and University of California at Los Angeles). Institutional review board approval was obtained at each site prior to subject enrollment.

To date, subjects have been prospectively interviewed weekly for a mean ± SD of 37.13 ± 20.4 weeks for 261.7 ± 94.1 weeks (approximately 5 years). At present, subject retention rate is 84.8%.

Procedures

Children and parents were 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),[15] the Kiddie Mania Rating Scale,[16] and the depression section of the K-SADS-PL.

Parents were interviewed at intake about their personal psychiatric history by using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I),[17] and about their first- and second-degree psychiatric family history by using a modified version of the Family History Screen.[18] Socioeconomic status was measured using the Hollingshead 4-Factor Scale.[19] Functional impairment was assessed by using the Child Global Assessment Scale,[20] and the child and parent Screen for Child Anxiety Related Emotional Disorder[21] was used to evaluate severity of anxiety.

Longitudinal changes in psychiatric symptoms, functioning, and treatment exposure since the previous evaluation were assessed by using the Longitudinal Interval Follow-Up Evaluation.[22,23] The Longitudinal Interval Follow-Up Evaluation evaluates the course of symptoms by identifying change points, frequently anchored by memorable dates for the subject (eg, holidays, beginning of school). The severity of ongoing symptoms, onset of new symptoms, and episode polarity for bipolar disorder since the last appointment are tracked by using weekly Longitudinal Interval Follow-Up Evaluation Psychiatric Status Rating scores. For *DSM-IV* mood disorders, the Psychiatric Status Rating scores range from 1 for no symptoms, to 2 to 4 for varying levels of subthreshold symptoms and impairment, to 5 or 6 for full criteria with different degrees of severity or impairment. Most of the anxiety disorders were also rated on a 6-point scale of 1 to 6, on which 5 and 6 indicate presence of *DSM*-threshold symptoms. Some anxiety disorders (anxiety NOS and separation anxiety disorder), other comorbid disorders, and psychosis were assigned weekly scores on a 3-point scale of 1 to 3, on which 3 indicates presence of *DSM*-threshold symptoms. A past history of subsyndromal anxiety was defined as youth with 75% of the *DSM-IV* criteria for any anxiety disorder and functional impairment and was ascertained through K-SADS-PL completed at intake. Youth with only specific phobia (eg, fear of the dark) were excluded because simple phobias are ubiquitous.[3] At intake, information about past and current pharmacologic treatment was obtained. Information about pharmacologic treatment during the follow-up was ascertained by using the Psychotropic Treatment Record of the Longitudinal Interval Follow-Up Evaluation. Each specific type of treatment and dose was recorded on a weekly basis.

Definition of Persistence of Anxiety Disorders

The mean ± SD of the distribution of time with anxiety disorders during the follow-up was 56.9 ± 33 weeks, with a median of 55.4 weeks. On the basis of this distribution, persistence of anxiety disorders over the follow-up period was defined as at least 50% of follow-up time meeting full-threshold *DSM-IV* anxiety disorders criteria.

Definition of Remission

Neither the *DSM-IV* nor the pediatric literature provides a definition of remission for anxiety disorders. Therefore, we used the criteria described in the adult literature of remission for anxiety disorders that is similar to the definition used for depression, namely, at least 8 consecutive weeks with only 1 or 2 symptoms to a mild degree.[24–26] To avoid overlap with the anxiety disorders present at intake, onset of new anxiety disorders were counted only if they started more than 8-weeks after intake.

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Table 1. Demographic and Clinical Characteristics at Intake Associated With the Persistence of Anxiety Disorders in Youth With Bipolar Disorder Based on the Percentage of Time Spent With Anxiety Disorders

Variable	≤ 50% Time in Anxiety (n = 67)	> 50% Time in Anxiety (n = 70)	Statistic	*P* Value
Demographic				
Age, mean ± SD, y	12.8 ± 3.2	12.4 ± 3.5	$t = 0.77$	.4
Female sex, %	40.3	54.3	$\chi^2 = 2.69$	.1
White, %	88.1	80.0	$\chi^2 = 1.65$	.2
Socioeconomic status, mean ± SD[a]	3.4 ± 1.1	3.1 ± 1.2	$t = 1.5$	.1
Living with both natural parents, %	40.3	35.7	$\chi^2 = 0.31$	.6
Clinical				
Bipolar disorder subtype, %				
I	64.2	47.1	$\chi^2 = 4.03$	.1
II	8.9	12.9		
Not otherwise specified	26.9	40.0		
Age at onset of mood symptoms, mean ± SD, y[b]	7.9 ± 3.5	7.8 ± 4.2	$t = 0.2$	.8
Duration of bipolar disorder, mean ± SD, y[c]	4.9 ± 3.1	4.7 ± 3.3	$t = 0.43$	.7
Mania Rating Scale score, mean ± SD				
Current	22.5 ± 11.5	25.3 ± 12.7	$t = 1.37$	.2
Most severe lifetime	35.6 ± 8.0	35.3 ± 8.2	$t = 0.2$	.8
Depression Rating Scale score, mean ± SD				
Current	17.3 ± 9.6	18.6 ± 10.1	$t = 0.75$	.5
Most severe lifetime	25.0 ± 10.0	25.1 ± 10.0	$t = 0.02$	> .9
Age at onset of anxiety disorder, mean ± SD, y	6.6 ± 3.1	5.8 ± 3.0	$t = 1.6$	.1
Anxiety disorders subtype, %				
Separation anxiety disorder	50.8	60.0	$\chi^2 = 1.19$	.3
GAD	31.3	48.6	$\chi^2 = 4.23$	.04
OCD	11.9	18.6	$\chi^2 = 1.16$	.3
PTSD	14.9	12.9	$\chi^2 = 0.12$	.7
Social phobia	11.9	18.6	$\chi^2 = 1.16$	.3
Panic disorder	11.9	15.7	$\chi^2 = 0.41$	.5
Agoraphobia	3.0	10.0	Fisher exact	.2
Anxiety not otherwise specified	4.5	2.9	Fisher exact	.7
≥ 2 Anxiety disorders, %	34.3	58.6	$\chi^2 = 8.08$	.005
Screen for Child Anxiety Related Emotional Disorder score, mean ± SD				
Child	30.2 ± 17.3	35.3 ± 18.4	$t = 1.55$	.1
Parent	33.1 ± 16.3	36.3 ± 16.4	$t = 1.13$	.3
ADHD, %	58.2	61.4	$\chi^2 = 0.15$	.7
Oppositional defiant disorder, %	35.8	34.3	$\chi^2 = 0.04$	.9
Conduct disorder, %	13.4	5.7	$\chi^2 = 2.38$	.1
Substance use disorder, %	4.5	7.1	Fisher exact	.7
Suicide attempt, %	35.8	30.0	$\chi^2 = 0.53$	.5
History of physical or sexual abuse, %	26.9	25.7	$\chi^2 = 0.02$	.9
Psychotic symptoms, %	31.3	24.3	$\chi^2 = 0.85$	.4
Child Global Assessment Scale score, mean ± SD				
Current	55.7 ± 11.3	55.4 ± 9.9	$t = 0.16$	.9
Most severe lifetime	39.0 ± 10.9	35.5 ± 11.9	$t = 1.75$	.08
Lifetime pharmacologic treatment, %				
Any psychotropics	97.0	95.7	Fisher exact	> .9
Antimanics	89.6	75.7	$\chi^2 = 4.54$	.03
Antidepressants	62.7	68.6	$\chi^2 = 0.53$	.5
Stimulants	58.2	57.1	$\chi^2 = 0.02$	.9
Psychiatric family history (at least 1 first- or second-degree relative), %				
Mania/hypomania	49.3	60.0	$\chi^2 = 1.6$	.2
Depression	85.1	92.9	$\chi^2 = 2.13$	.1
ADHD	43.3	45.7	$\chi^2 = 0.08$	.7
Conduct disorder	38.8	35.7	$\chi^2 = 0.14$	.7
Anxiety disorder	71.6	78.6	$\chi^2 = 0.88$	.3
Schizophrenia	7.5	10.0	$\chi^2 = 0.28$	.6
Any substance use disorder	68.7	71.4	$\chi^2 = 0.13$	.7
Suicide attempt	40.3	45.7	$\chi^2 = 0.41$	.5

[a]Hollingshead 4-Factor Scale. [b]Age 4 is set as the minimum value. [c]Since age at onset of any *DSM* mood episode.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAD = generalized anxiety disorder, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

Statistical Analyses

Analyses of the persistence of anxiety disorders included between-group comparisons using *t* tests or χ^2 tests as appropriate. As is customary,[27] and given that this is the first study prospectively evaluating anxiety disorders in youth with bipolar disorder, intake and follow-up variables with *P* values < .1 associated with the persistence of anxiety disorder were entered into a stepwise logistic regression and controlled for between-group significant demographic variables.

Analyses of the factors associated with the onset of new anxiety disorders in bipolar disorder youth were performed by using the log-rank test or Cox proportional hazards

Table 2. Follow-Up Factors Associated With the Persistence of Anxiety Disorders in Youth With Bipolar Disorder Based on the Percentage of Time Spent With Anxiety Disorders[a]

Factor	≤ 50% Time in Anxiety (n = 67)	> 50% Time in Anxiety (n = 70)	*t*	*P* Value
% Weeks in mood state				
Euthymia	41.5 ± 26.4	25.2 ± 22.3	3.91	< .001
Any subthreshold mood state (depression or mania/hypomania)	41.8 ± 23.2	50.9 ± 25.2	2.20	.03
Full threshold depression	12.3 ± 14.0	18.0 ± 19.1	2.00	.05
Full threshold of mania/hypomania	4.5 ± 9.2	5.9 ± 9.2	0.92	.4
Any full threshold mood state (depression or mania/hypomania)	16.7 ± 18.1	23.9 ± 22.0	2.08	.04
% Weeks meeting full diagnostic criteria for a comorbid condition				
Any comorbid disorder	53.0 ± 37.9	66.7 ± 40.8	2.03	.05
ADHD	43.5 ± 38.1	56.8 ± 45.0	1.86	.07
Conduct disorder	6.8 ± 16.6	2.5 ± 12.0	1.72	.09
Oppositional defiant disorder	20.3 ± 32.4	28.6 ± 37.8	1.38	.2
Substance use disorder	5.1 ± 15.4	9.9 ± 21.5	1.51	.2
Psychosis	3.9 ± 10.5	3.7 ± 13.3	0.10	.9
% Weeks receiving psychopharmacologic treatment				
Any psychotropics	75.3 ± 31.3	74.2 ± 37.8	0.20	.9
Antimanics	64.0 ± 37.4	61.6 ± 41.4	0.36	.7
Antidepressants	34.5 ± 36.7	24.1 ± 33.4	1.74	.08
Stimulants	26.3 ± 33.9	25.0 ± 39.3	0.20	.8
% Weeks receiving other services				
Any psychosocial	43.8 ± 26.1	47.5 ± 28.0	0.79	.4
Inpatient/residential	4.8 ± 8.2	4.3 ± 10.7	0.32	.7
Specialized psychosocial	13.9 ± 18.8	17.4 ± 26.9	0.90	.4
Outpatient	34.5 ± 23.5	32.0 ± 22.8	0.63	.5

[a]Factors are presented as mean ± SD.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

regressions. A Cox proportional hazards regression with time-varying covariates was used to identify factors that occurred during prospective follow-up and were associated with onset of new anxiety disorders. Data for the time-varying covariates were ascertained with the Longitudinal Interval Follow-Up Evaluation. Weekly values on the Psychiatric Status Rating for individual diagnostic factors were aggregated over 8-week time intervals. A stepwise multivariate Cox regression analysis was performed including all variables with significance ($P < .1$) and controlled for any between-group significant demographic variables.

Odds ratios (ORs) and confidence intervals (CIs) were computed. All *P* values are based on 2-tailed tests, with $\alpha = .05$.

RESULTS

Before analyzing the persistence of anxiety during the follow-up, we performed analyses to ascertain the presence of any anxiety at any time during the follow-up and whether the anxiety disorders during the follow-up were of the same type as those present at intake. At any time during the follow-up, 80.6% (137/170) of the youth had an anxiety disorder (GAD, 49.6%; separation anxiety disorder, 44.5%; social phobia, 34.3%; OCD, 27.7%; panic disorder, 21.2%; PTSD, 15.3%; anxiety NOS, 15.3%; and agoraphobia, 11%). Fifty-three-percent of youth with any anxiety disorders had ≥ 2 anxiety disorders. Youth diagnosed with a given anxiety disorder at intake tended to have the same disorder over the follow-up (OCD, 90.5%; social phobia, 85.7%; GAD, 83.6%; anxiety NOS, 80%; agoraphobia, 77.8%; panic disorder, 73.7%; separation anxiety disorder, 69.7%; and PTSD, 57.9%).

Of the 137 youth who continued to have any anxiety disorder, 67 subjects spent ≤ 50% of the follow-up time with anxiety disorders, and 70 subjects spent more than 50% of the follow-up time with anxiety disorders.

Intake and Follow-Up Factors Associated With the Persistence of Anxiety

For the intake factors, univariate analyses showed that bipolar disorder youth with persistent anxiety were significantly more likely to have ≥ 2 comorbid anxiety disorders, GAD, and less lifetime treatment with antimanic medications (Table 1; all *P* values ≤ .05). In addition, analyses of medication used at intake showed less treatment with antimanic medications (80.6% vs 62.9%; $\chi^2 = 5.3$; $P = .02$; data not included in the Table).

For the follow-up factors, univariate analyses showed that bipolar disorder youth with persistent anxiety had significantly less follow-up time in euthymia, more subthreshold and threshold mood symptoms, more full-threshold depression, and more follow-up time spent with any comorbid disorder (Table 2; all *P* values ≤ .05).

Multivariate regression analyses for the intake and follow-up factors showed that persistent anxiety was associated with having ≥ 2 comorbid anxiety disorders (OR = 2.14; 95% CI, 1.03–4.47; $P = .04$), less antimanic treatment at intake (OR = 0.37; 95% CI, 0.16–0.85; $P = .02$), less follow-up time spent euthymic (OR = 0.97; 95% CI, 0.96–0.99; $P = .0004$), less ongoing conduct disorder (OR = 0.96; 95% CI, 0.94–0.99; $P = .01$), and less follow-up time receiving antidepressant medications (OR = 0.99; 95% CI, 0.98–1.00; $P = .04$).

Prevalence of Onset of New Anxiety Disorders

Of the 243 youth who at intake did not have any lifetime *DSM-IV* anxiety disorders, 60 (24.7%) had an onset of new disorders, including GAD, 31.7%; anxiety NOS, 28.3%;

Table 3. Demographic and Clinical Characteristics at Intake Associated With the Onset of New Anxiety Disorders in Youth With Bipolar Disorder

Variable	Bipolar Disorder With New-Onset Anxiety (n = 60)	Bipolar Disorder Without Anxiety (n = 157)	χ^2	*P* Value
Demographic				
Age, mean ± SD, y	12.5 ± 3.3	12.7 ± 3.2	0.58	.4
Female sex, %	58.3	43.3	2.98	.09
White, %	75.0	83.4	2.78	.1
Socioeconomic status, mean ± SD	3.3 ± 1.1	3.6 ± 1.2	5.13	.02
Living with both natural parents, %	35.0	49.0	3.83	.05
Clinical				
Bipolar disorder subtype, %				
I	53.3	62.4	1.88	.4
II	8.3	3.8		
Not otherwise specified	38.3	33.7		
Age at onset of mood symptoms, mean ± SD, y[a]	8.5 ± 3.8	9.0 ± 4.3	1.03	.3
Duration of bipolar disorder, mean ± SD, y[b]	4.0 ± 2.6	3.7 ± 2.5	0.49	.5
Mania Rating Scale score, mean ± SD				
Current	23.3 ± 10.4	22.2 ± 12.6	0.20	.7
Most severe lifetime	33.1 ± 6.1	33.7 ± 9.0	0.10	.8
Depression Rating Scale score, mean ± SD				
Current	14.1 ± 9.1	10.8 ± 9.5	3.69	.06
Most severe lifetime	23.4 ± 10.3	19.4 ± 11.3	3.13	.08
Child Global Assessment Scale score, mean ± SD				
Current	56.1 ± 11.3	54.1 ± 13.8	0.84	.4
Most severe lifetime	39.4 ± 12.1	37.4 ± 9.0	1.47	.3
Screen for Child Anxiety Related Emotional Disorder score, mean ± SD				
Child	23.2 ± 13.8	18.4 ± 17.5	3.92	.05
Parent	23.0 ± 12.8	15.7 ± 12.2	13.70	< .001
ADHD, %	63.3	55.4	1.91	.2
Oppositional defiant disorder, %	40.0	44.0	0.17	.7
Conduct disorder, %	18.3	10.2	3.99	.05
Any subsyndromal anxiety, %	26.7	15.3	4.19	.04
Substance use disorder, %	16.7	5.7	6.43	.01
Suicide attempt, %	35.0	21.7	3.20	.07
History of physical or sexual abuse, %	25.0	10.8	6.66	.01
Psychotic symptoms, %	21.7	19.8	0.001	.9
Lifetime pharmacologic treatment, %				
Any psychotropics	91.7	96.2	1.29	.3
Antimanics	68.3	84.7	7.37	.007
Antidepressants	55.0	42.7	1.93	.2
Stimulants	60.0	52.9	1.27	.26
Psychiatric family history (at least 1 first- or second-degree relative), %				
Mania/hypomania	53.3	42.7	1.49	.2
Depression	78.3	74.5	0.34	.6
ADHD	40.0	35.7	0.49	.5
Conduct disorder	31.7	26.1	1.1	.3
Anxiety disorder	58.3	57.3	0.02	.9
Schizophrenia	3.3	2.6	0.23	.6
Any substance use disorder	66.7	64.3	0.29	.6
Suicide attempt	33.3	38.2	0.15	.7

[a]Age 4 is set as the minimum value. [b]Since age at onset of any *DSM* mood episode.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

PTSD, 20%; social phobia, 18.3%; OCD, 15%; panic disorder, 11.7%; separation anxiety disorder, 10%; and agoraphobia, 3.3%. Eighteen percent of subjects with any new anxiety disorder had new onset of ≥ 2 anxiety disorders.

Intake and Follow-Up Factors Associated With Onset of New Anxiety Disorders

For the intake factors, univariate analyses showed that new-onset anxiety disorders were significantly associated with lower socioeconomic status, not living with both natural parents, and higher total scores on the child's and parent's Screen for Child Anxiety Related Emotional Disorder. In addition, conduct disorder, substance use disorders, history of physical or sexual abuse, history of subsyndromal anxiety, and less lifetime antimanic medications were significantly associated with new onset of anxiety (Table 3; all *P* values ≤ .05). Additional analyses of medications used at the time of the intake showed that use of stimulants was associated with the onset of more new anxiety disorders (36.7 vs 24.2; χ^2=3.9; *P* = .05; data not included Table 3).

For the follow-up factors, univariate analyses showed that onset of new anxiety disorders was significantly associated with less time euthymic, more time in depression and mania/hypomania, ADHD, conduct disorder, substance use disorders, and less time receiving antimanic medications (Table 4; all *P* values ≤ .05).

Table 4. Follow-Up Factors Associated With the Onset of New Anxiety Disorders in Youth With Bipolar Disorder[a]

Factor	Bipolar Disorder With New-Onset Anxiety (n = 60) Time 1[b]	Time 2[c]	Bipolar Disorder Without Anxiety (n = 157)	χ^2	*P* Value
% Weeks in mood state					
Euthymia	43.3 ± 38.7	39.5 ± 29.5	55.4 ± 31.0	3.80	.05
Any subthreshold mood state (depression or mania/hypomania)	36.7 ± 38.6	43.1 ± 28.7	34.6 ± 27.5	0.007	.9
Full threshold depression	10.4 ± 25.9	11.7 ± 21.7	5.7 ± 11.7	3.92	.05
Full threshold of mania/hypomania	9.6 ± 23.6	5.6 ± 9.8	4.2 ± 10.9	6.92	.009
Any full threshold mood state (depression or mania/hypomania)	20.0 ± 33.0	17.3 ± 21.9	9.9 ± 16.4	10.64	.001
% Weeks meeting full diagnostic criteria for a comorbid condition					
Any comorbid disorder	75.4 ± 41.9	72.3 ± 38.9	52.2 ± 39.8	12.30	.001
ADHD	59.6 ± 48.7	59.6 ± 45.3	45.0 ± 41.8	6.12	.01
Conduct disorder	11.5 ± 31.2	11.7 ± 27.3	6.3 ± 21.0	4.77	.03
Oppositional defiant disorder	24.4 ± 40.2	26.5 ± 33.5	22.8 ± 33.7	0.27	.6
Substance use disorders	17.3 ± 36.6	13.0 ± 27.2	4.8 ± 13.8	12.48	< .001
Psychosis	3.3 ± 17.0	2.7 ± 10.9	1.1 ± 5.1	2.29	.1
% Weeks receiving psychopharmacologic treatment					
Any psychotropics	64.8 ± 47.2	76.0 ± 34.1	73.7 ± 33.9	1.79	.2
Antimanics	46.9 ± 49.3	61.0 ± 41.3	61.7 ± 38.8	4.36	.04
Antidepressants	8.1 ± 27.2	11.7 ± 26.8	13.4 ± 26.5	1.38	.2
Stimulants	24.6 ± 42.2	25.7 ± 39.4	22.6 ± 36.4	0.12	.7
% Weeks receiving other services					
Any psychosocial	42.7 ± 41.4	42.9 ± 31.5	40.4 ± 30.2	0.82	.4
Inpatient/residential	4.2 ± 15.9	4.8 ± 12.1	4.5 ± 13.6	0.001	> .9
Specialized psychosocial	17.5 ± 36.0	16.4 ± 27.5	11.5 ± 24.2	2.20	.1
Outpatient	31.9 ± 33.1	32.6 ± 25.7	30.6 ± 25.0	0.49	.5

[a]Factors are presented as mean ± SD. [b]Eight weeks prior to anxiety. [c]Prior to Time 1.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Multivariate regression analyses for the intake and follow-up factors showed that onset of new anxiety disorders was associated with being female (hazard ratio [HR]: 1.81; 95% CI, 1.05–3.11; *P* = .03), lower socioeconomic status (HR: 0.8; 95% CI, 0.65–0.99; *P* = .05), stimulant treatment at intake (HR: 1.91; 95% CI, 1.09–3.34; *P* = .02), ongoing ADHD (HR: 1.01; 95% CI, 1.002–1.01; *P* = .01) and substance use disorders (HR: 1.01; 95% CI, 1.003–1.02; *P* = .004), and more follow-up time with manic/hypomanic symptoms (HR: 1.01; 95% CI, 1.001–1.02; *P* = .04).

As noted above, use of stimulants was 1 of the intake factors associated with onset of new anxiety disorders. To disentangle the effects of stimulants and ADHD, both variables were entered into a regression. In this analysis, only ADHD was associated with the onset of new of anxiety disorders (*P* = .05).

DISCUSSION

To our knowledge, this is the first study examining the long-term outcome of anxiety disorders and the factors that predict onset of new anxiety disorders among youth with bipolar disorder. Present findings indicate that most anxiety disorders diagnosed at intake continued during the follow-up and were of the same type. Moreover, about 50% of the youth had persistent anxiety, particularly GAD. The persistence of anxiety disorders was associated with multiple anxiety disorders, less follow-up time euthymic, less comorbid conduct disorder, and less treatment with antimanic and antidepressant medications. Twenty-five percent of the sample who did not have an anxiety disorder at intake developed new anxiety disorders during follow-up, most commonly GAD. The onset of new anxiety disorders was significantly associated with being female, lower socioeconomic status, presence of ADHD and substance use disorders, and more follow-up time with manic or hypomanic symptoms.

Since no other pediatric and adult longitudinal studies that have assessed the outcome of anxiety disorders in bipolar disorder, we compared our results with existing literature on the course of anxiety disorders in youth and adults without bipolar disorder. Similar to our findings, results from longitudinal studies in youth with anxiety disorders have also shown that, with the exception of separation anxiety disorder, most anxiety disorders, and especially GAD,[24,25,28,29] tend to continue into adulthood.[29–32] Also, evidence for the homotypic continuation of the anxiety disorders has been reported,[33,34] and, in concordance with our results, multiple anxiety disorders[35] predicted higher persistence of anxiety disorders. In contrast with other studies[36,37] which mainly included males, we found that persistence of anxiety was associated with less comorbid conduct disorder. This finding might be explained by the fact that there were no differences in the proportion of males and females in the Course of Outcome of Bipolar Youth study.[38] The persistence of anxiety over time may explain in part the high association between anxiety disorders and bipolar disorder and could be a unique factor that negatively influences bipolar disorder severity and prognosis[6–8,11] compared to other comorbid conditions such as ADHD and substance use disorders. Furthermore, our results and those of 1 epidemiologic study in youth[39] give evidence that the relationship between anxiety disorders and bipolar disorder

severity may be bidirectional, as ongoing symptoms of mania or hypomania are associated with persistence and the onset of new anxiety disorders.

The results of our study together with the fact that pediatric anxiety disorders may continue into adulthood and that anxiety disorders worsen the course of bipolar disorder[6,7] indicate the need for early identification and treatment of these disorders in youth with bipolar disorder. Current evidence-based treatments for anxiety disorders show that cognitive-behavioral therapy (CBT) and the selective serotonin reuptake inhibitors (SSRIs), and in particular their combination, are efficacious for the acute treatment of anxiety in youth.[40] Although we know that CBT is efficacious for youth with anxiety disorders, youth with comorbid bipolar disorder have been excluded from these trials, and thus we do not have data on its efficacy for this population. Moreover, even if the SSRIs are efficacious and well tolerated for youth with anxiety, we do not know the efficacy and tolerability of these medications for youth with bipolar disorder and anxiety. Since there are no randomized controlled trials comparing CBT, SSRIs, or the combination of both treatments in youth (and adults) with anxiety and bipolar disorder, we feel these studies are necessary. Such studies would inform clinical practice, and answer a very important question about the relative efficacy of CBT, SSRIs, and/or the combination, for youth with the common and impairing presentation of comorbid bipolar disorder and anxiety.

About one-quarter of the sample developed new anxiety disorders during the follow-up. Similar to findings in the pediatric and adult literature, female sex[41,42] and lower socioeconomic status[41,43] increased the risk for new anxiety disorders, particularly GAD.[41,44] Our findings are also consistent with the epidemiologic literature in which anxiety disorders are more prevalent in females,[30,43] especially GAD in adolescent females.[41,45]

Epidemiologic as well as clinical studies have shown that youth[46–49] and adults[50,51] with bipolar disorder are at high risk for substance use disorders. Also, both bipolar disorder and substance use disorders are strongly associated with anxiety.[52] Similarly, our findings showed that bipolar disorder youth with substance use disorders or ADHD[53] were at high risk for onset of new anxiety disorders, suggesting that early recognition and treatment of these disorders may prevent the development of new anxiety disorders.

These above-noted results need to be taken in the context of the limitations of this study. First, no psychiatric control group was included. Thus, we cannot conclude that anxiety disorders are more common in youth with bipolar disorder than in youth with other childhood psychiatric disorders (eg, major depressive disorder). However, other pediatric and adults studies have consistently shown that anxiety disorders are more common in bipolar disorder than in other psychiatric disorders.[54,55] Second, the effects of treatment were not analyzed. Finally, since subjects were a referred sample, findings may not apply to other populations.

In summary, most anxiety disorders persisted during the follow-up and a substantial group of subjects developed new anxiety disorders. Consistent with the literature for other disorders (eg, major depressive disorder),[56] we found that different factors were associated with the persistence and the onset of new anxiety disorders. Early identification and appropriate management of these risk factors may improve the course of bipolar disorder youth. Randomized controlled trials are warranted to evaluate whether existing treatments known to be efficacious for anxiety disorders particularly psychosocial treatments, such as CBT, that are not associated with inducing mood instability, are equally efficacious and tolerable for youth with comorbid bipolar disorder and anxiety disorders.

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