Negative Life Events in Children and Adolescents With Bipolar Disorder

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Objective: To study the relationship between negative life events and demographic and clinical variables in youth with bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified (NOS), as well as to compare the rates of life events in youth with bipolar disorder, depressive and/or anxiety disorders (DEP-ANX), and healthy controls.

Method: Subjects included 446 youth, aged 7 to 17 years, meeting *DSM-IV* criteria for bipolar I, bipolar II, or an operationalized definition of bipolar disorder NOS, and were enrolled in the Course and Outcome of Bipolar Illness in Youth study. Subjects completed the Life Events Checklist. Sixty-five DEP-ANX and 65 healthy youth were obtained from previous studies using similar methodology. The study was conducted from October 2000 to July 2006.

Results: Older age, lower socioeconomic status, living with nonintact family, non-Caucasian race, anxiety, and disruptive disorders were associated with greater number of total negative life events. Specifically, increased independent, dependent, and uncertain negative life events were associated with lower socioeconomic status, nonintact family, and comorbid disruptive disorders. Increased independent negative life events were additionally associated with non-Caucasian race and comorbid anxiety disorders. Increased dependent and uncertain negative life events were also associated with older age. DEP-ANX youth reported a similar rate of negative life events as bipolar youth, and both groups had more negative life events than the healthy controls. Bipolar youth reported fewer total and dependent positive life events compared to DEP-ANX and healthy youths.

Conclusions: Similar to DEP-ANX youth, bipolar youth are exposed to excessive negative independent and dependent life events, which may have implications in the long-term outcome and negative consequences associated with this disorder.

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Studies of negative life events in adults with mood disorders have found that exposure to negative life events plays a significant role in the onset and maintenance of mood disorders.[1,2] Specifically, for bipolar disorder, studies have found that bipolar adults experience increased severe negative life events prior to the onset and recurrences of depressive and manic episodes.[3,4]

A significant body of literature has also studied the effects of stress in depressed children and adolescents.[5] Studies in clinical populations have shown that unipolar depressed adolescents have significantly more negative life events than healthy controls and anxious children.[6–8] In addition, disappointing events (eg, failing grades, breaking up with boyfriend/girlfriend, losing a job) and ongoing family conflicts are associated with persistent general psychopathology or recurrent depression.[9,10] Similarly, studies including community samples have shown that stressful life events such as difficulties with academics or peers predicted internalizing syndromes.[11]

The study of stressful life events in children and adolescents with bipolar disorder is essential to understand the impact that psychosocial stressors have on the course and outcome of the illness and to aid in the development of strategies to help these youth avoid or cope with psychosocial stressors. However, there are very few studies that have examined the role of life events in pediatric bipolar disorder. This topic is particularly important in light of recent findings showing a significant association between genetic predisposition to depression and exposure to negative life events.[12–14] Furthermore, subjects with mood disorders are also more likely to generate so-called "dependent life events" that are putatively associated with their behavior (stress generation model), and these dependent life events may play a role in the chronicity of the mood disorder.[15] For example, subjects with subsyndromal symptoms of depression and anxiety are more likely to experience stressful life events that may, at least in part, account for their increased risk to develop full syndromic depressive episodes.[16] Finally, stressful events can also alter daily routines and rhythms (eg, sleep), and the disruption of these rhythms may trigger an episode of depression or mania or destabilize a patient with bipolar disorder.[17]

The few studies that have examined life events among bipolar youth have shown that negative life events are significantly more common among bipolar youth when compared to youth with attention-deficit/hyperactivity disorder (ADHD)[18] or healthy controls.[18,19] In a retrospective chart review,[20] specific negative life events such as abuse, neglect, or foster care placement have been associated with increased psychiatric hospitalizations, delay of diagnosis, and decreased response to treatment. Kim and colleagues[21] recently published a prospective study with 38 bipolar adolescents enrolled in a psychosocial program. They found that chronic stress in intimate relationships predicted less improvement in mania, depression, and mixed mood symptoms.

The above noted results suggest that exposure to negative life events may be associated with the onset and perhaps negatively affect the course of bipolar disorder in youth. However, in addition to the small number of studies, most of the existing literature has methodological limitations, such as small samples, mainly including adolescents with bipolar I disorder, and not controlling for the effects of sociodemographic factors or comorbid disorders.

In a prior study, we reported a lifetime prevalence of physical and sexual abuse in approximately 20% of youth with bipolar spectrum disorders.[22] Abuse was associated with living with a nonintact family, lifetime history of psychosis, comorbid posttraumatic stress disorder and conduct disorder, and first-degree family history of mood disorder. The goal of this study was to evaluate the prevalence of other types of negative life events in youth with bipolar spectrum disorder (bipolar I, bipolar II, and bipolar not otherwise specified [NOS]) and to study the relationship between negative life events and demographic and clinical variables. A second goal was to compare the prevalence of these events with a historical sample of youth with depression and/or anxiety disorders and healthy controls who were recruited and assessed in a manner similar to the bipolar disorder sample.[23,24]

Based on previous literature, it was hypothesized that demographic variables such as older age, lower socioeconomic status, and female sex would be associated with a higher number of negative life events. We also expected that among the bipolar disorder group, subjects with comorbid Axis I disorders would exhibit a greater number of negative life events. Finally, we anticipated that bipolar youth would exhibit a greater number of negative life events compared to youth with depression/anxiety, and both groups would exhibit higher rates of negative life events when compared to healthy controls.

METHOD

Participants

Bipolar sample. Four hundred forty-six (446) youths, ages 7 to 17 years and 11 months (mean ± SD, 12.7 ± 3.2), fulfilling *DSM-IV*[25] criteria for bipolar I disorder (n = 260), bipolar II disorder (n = 32), and bipolar disorder NOS (n = 154), using the bipolar disorder NOS Course and Outcome of Bipolar Illness in Youth (COBY) criteria,[26] were recruited from outpatient and inpatient units at the University of Pittsburgh, Brown University, and UCLA. Because the *DSM-IV* definition of bipolar disorder NOS is vague, COBY operationalized the diagnosis of bipolar disorder NOS as a *minimum* of the following symptoms: (1) elated mood, plus 2 associated *DSM-IV* symptoms, or irritable mood plus 3 *DSM-IV* associated symptoms; (2) change in the level of functioning; (3) duration of a minimum of 4 hr within a 24-hr period; and (4) at least 4 cumulative lifetime days meeting the criteria. Children and adolescents with bipolar disorder NOS have been shown to have similar clinical pictures, comorbid disorders, family history, and longitudinal outcome as youth with bipolar I disorder.[27] Moreover, approximately 30% of youth with bipolar disorder NOS, especially those with elevated family history of bipolar disorder, converted into bipolar I or II disorder.[26] About 70% of the sample were recruited from outpatient clinics. Inclusion and exclusion criteria are described elsewhere.[26,27] The study was conducted from October 2000 to July 2006.

As shown in Table 1, bipolar II participants were significantly older (mean ± SD, 14.7 ± 2.8 years) than bipolar I participants (12.8 ± 3.2 years), and both groups were significantly older than bipolar NOS participants (11.9 ± 3.3 years) (all P values < .05). There were no statistically significant differences in sex (47% female), socioeconomic status (3.4 ± 1.2 middle class), race (81% Caucasian), or living situation (42% living with both biologic parents) among the 3 bipolar subgroups. At intake, 14% of the sample was asymptomatic and 86% were symptomatic (64% full episode and 22% in partial remission). There were no statistically significant differences in the rates of lifetime comorbid disorders except for anxiety disorders. Bipolar II subjects were more likely to have comorbid anxiety disorders than bipolar I subjects (P = .04).

The institutional review board at each of the participating sites approved this study. Informed consent was obtained prior to initiation of the assessment from the participant's parent/guardian and from participants aged 14 and older. The study procedures were explained in age-appropriate language to younger participants and verbal assent was obtained prior to the assessment.

Historical controls. In order to contrast the life events of the bipolar disorder sample with other groups, 2 historical samples were obtained from 2 previous studies conducted at the University of Pittsburgh.[23,24] These studies used similar methodology to ascertain life events and psychiatric diagnoses as COBY (see Instruments section below). Moreover, the same team of child and adolescent psychiatrists participating in the Pittsburgh COBY site conducted these studies. The historical sample consisted of 65 children and adolescents with depression and/or anxiety disorders

Table 1. Demographic and Clinical Characteristics for Bipolar Disorder Subjects

Characteristic	Bipolar I (n = 260)	Bipolar II (n = 32)	Bipolar NOS (n = 154)	Statistic	Overall *P* Value
Age, mean ± SD, y	12.8 ± 3.2[a]	14.7 ± 2.8[b]	11.9 ± 3.3[c]	$F_{2,443} = 10.8$	< .0001
Sex, female, %	48.5	59.4	41.6	$\chi^2 = 4.0$	NS
Race, Caucasian, %	80.4	84.4	82.5	$\chi^2 = 0.5$	NS
Socioeconomic status, mean ± SD	3.4 ± 1.3	3.8 ± 0.9	3.5 ± 1.1	$\chi^2 = 2.6$ [d]	NS
Living with both natural parents, %	38.1	53.1	44.8	$\chi^2 = 3.7$	NS
Comorbidity, lifetime, %					
ADHD	61.2	43.8	61.7	$\chi^2 = 3.8$	NS
ODD	40.8	21.9	40.9	$\chi^2 = 4.5$	NS
Conduct disorder	13.1	12.5	11.7	$\chi^2 = 0.2$	NS
Substance abuse/dependence	9.2	6.3	9.1	$\chi^2 = 0.3$	NS
Anxiety disorder	38.8[a]	62.5[b]	40.3[a,b]	$\chi^2 = 6.6$	.04

[a,b,c]Means with different superscripts are significantly different, with *P* values ≤ .05.
[d]Statistic obtained by Kruskal-Wallis test.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NOS = not otherwise specified, NS = not significant, ODD = oppositional defiant disorder.

Table 2. Demographic Characteristics for Bipolar Disorder, DEP-ANX, and Healthy Control Subjects

Characteristic	Bipolar Disorder (n = 446)	DEP-ANX (n = 65)	Healthy Controls (n = 65)	Statistic	Overall *P* Value
Age, mean ± SD, y	12.7 ± 3.3[a]	14.2 ± 2.5[b]	14.3 ± 2.1[b]	$F_{2,573} = 13.5$	< .0001
Sex, female, %	46.9[a]	64.6[b]	56.9[a,b]	$\chi^2_2 = 8.6$	.01
Race, Caucasian, %	81.4	86.2	89.2	$\chi^2_2 = 3$	NS

[a,b]Means with different superscripts are significantly different, with *P* values ≤ .05.
Abbreviations: DEP-ANX = depressive and/or anxiety disorder, NS = not significant.

(DEP-ANX) and 65 healthy controls aged 8 to 18 years. Details regarding the assessment of these subjects were described in their respective articles.[23,24] Briefly, the group with DEP-ANX spectrum included 35 adolescents aged 13 to 18 years with major depressive disorder[23] and 30 children and adolescents aged 8 to 17 years old with depressive or anxiety disorders.[24]

The healthy control group included 35 adolescents aged 13 to 18 years and 30 children and adolescents aged 8 to 17 years recruited from the general community and screened for the absence of any Axis I psychopathology.[23,24]

As shown in Table 2, there were no differences in age between the DEP-ANX and healthy controls, but both groups were significantly older than the bipolar disorder subjects (14.2 ± 2.5 and 14.3 ± 2.1 vs 12.7 ± 3.3, respectively, $F_{2,573} = 13.5$, $P < .001$). Also, DEP-ANX subjects were more likely to be female (65%) than the bipolar disorder group (47%) ($\chi^2_2 = 8.6$, $P = .01$). There were no group differences in terms of race (83% Caucasian).

Instruments

The assessment of the youth with bipolar disorder was described in detail elsewhere.[26,27] Briefly, subjects and their primary caregivers were assessed about nonmood psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)[28] by a trained research clinician. Mood symptoms were assessed by the mood disorder sections of the K-SADS-Present Episode (K-SADS-P; 4th revision)[29] plus additional items from the Kiddie Mania Rating Scale.[30] Diagnostic reliability for all disorders was high (κ values ≥ 0.80). Similarly, participants and their primary caregivers in the DEP-ANX and healthy control groups were assessed using the K-SADS-P and K-SADS-PL by trained clinicians.[23,24]

At intake, both youth and parents were asked to complete the Life Event Check list (LEC)[31] for the year preceding the evaluation. The LEC is a modification of the Life Events Record (LER)[32] and contains 46 life events. The LEC deviates from the LER in that for each life event, the respondent is asked to indicate if the event was positive or negative and the degree to which the event was stressful or unpleasant (coded on a 4-point scale ranging from no effect to great effect). Units of measure yielded by the LEC include the total number of positive and negative life events as well as weighted total impact of positive and negative events. Two-week test-retest reliability of the LEC for children and adolescents has been reported to be 0.69 (positive events) and 0.72 (negative events) for simple unit weights and 0.71 (positive events) and 0.66 (negative events) using weighted impact scores.[33] Only those events rated as negative events were the primary focus of the present analyses. Three of the authors (B.B., D.E.W., and S.R.) independently classified each of the 46 items in the following way. Items were classified as life events that are independent of the child's behavior (eg, birth of a new brother or sister, death in the family), events that are more likely to be dependent on the child's behavior (eg, being suspended from school), or uncertain

events (eg, changing to a new school) that could be independent of or dependent on the child's behavior. Negative life events were analyzed both pooled together (as total life events) and separately, grouped by subcategories (dependent or independent on the child's behavior, or uncertain). Subjective impact ratings are summed separately for good and bad events to create positive life change and negative life change scores. There is no evidence that weighting is preferable to simple counts of experienced events.[34] In our sample, the results obtained when analyzing the number of negative life events (as counts) were similar to those from the analysis of weighted negative life events (based on severity ratings). Moreover, negative life events rated by respondents as having a "great impact" were highly correlated with the total number of negative life events ($r = .85$, $P < .001$). Therefore, we only present the analysis performed with the simple counts of life events.

Secondary analyses were performed on a subset of the more severe life events (eg, serious illness or death of a family member, parents divorced or separated, death of a close friend, major personal illness, abortion) to assess if the prevalence of those specific severe life events differed across the 3 groups (bipolar disorder, DEP-ANX, and healthy controls). Additional analyses investigated differences in the number of positive life events across those 3 diagnostic groups.

Socioeconomic status was measured using the Hollingshead 4-factor scale.[35]

Statistical Analyses

Statistical analyses were conducted using the SAS Institute SAS Version 9.1 (SAS Institute, Inc., Cary, North Carolina) and included descriptive statistics for all categorical and continuous variables. Between-group differences in the sociodemographic and clinical factors were assessed using analysis of variance models for the continuous variables and χ^2 tests for the categorical variables.

Life events were analyzed using regression models for count response data. The ordinary least squares methods, commonly used in the life events literature, are not appropriate for modeling count data. Because the primary outcome, the number of life events, is a count, nonlinear models based on the Poisson distribution and negative binomial distribution were fitted to the data.[36] The Poisson regression model (PRM) and the negative binomial regression model (NBRM) have the same mean structure and for zero overdispersion the NBRM reduces to the PRM. Likelihood ratio tests were developed for goodness-of-fit (comparing the likelihood for the model to the likelihood for the restricted model without regressors) and for overdispersion (comparing the likelihood for the PRM to the likelihood for the NBRM) for each fitted model. Likelihood ratio tests for overdispersion indicated that the NBRM seemed to fit the data better than PRM. All *P* values are based on 2-tailed tests with $\alpha = .05$. All models for count data were implemented using SAS PROC GENMOD.

RESULTS

Negative Life Events Within Bipolar Subjects

In general, parents' reports about the negative life events experienced by their children yielded similar results to the youths' reports (correlations were for total $r_s = 0.6$, independent $r_s = 0.5$, dependent $r_s = 0.5$, and uncertain $r_s = 0.4$; all *P* values < .001). Thus, unless there were any significant differences in the negative life events reports between parents and their children, in this article, we only included the negative life events reported by youth.

There were no differences between symptomatic versus asymptomatic participants at intake in the reported number of life events.

Demographic characteristics. We first conducted univariate regression models for count data for each of the life events variables (total, independent, dependent, and uncertain) with demographic characteristics as predictors. Each demographic variable was first entered into the model containing only the intercept to assess if it contributes to the explanation of the response. All variables with *P* values < .2 in the univariate analyses were included in multiple negative binomial regression models, adjusting for the effect of the other demographic predictors. The significance of the predictors was tested using Wald χ^2 statistics. Results of the adjusted analyses are summarized in Table 3.

Total negative life events. Negative binomial regression analysis for count data showed a significant effect for age ($\chi^2_1 = 8$, $P = .005$), socioeconomic status ($\chi^2_1 = 7.8$, $P = .005$), living situation ($\chi^2_1 = 8.7$, $P = .003$), and race ($\chi^2_1 = 3.8$, $P = .05$) on the number of total negative life events experienced. Specifically, older age, lower socioeconomic status, living with nonintact family, and non-Caucasian race were associated with higher prevalence of total negative life events. There were no significant effects of sex or bipolar subtype on the number of reported life events.

Independent negative life events. The results of the negative binomial analysis indicated statistically significantly associations of lower socioeconomic status ($\chi^2_1 = 7.3$, $P = .007$), nonintact family ($\chi^2_1 = 6.6$, $P = .01$), and non-Caucasian race ($\chi^2_1 = 4.3$, $P = .04$) with higher frequency of negative independent life events. There were no effects of sex, bipolar subtype, or age on the number of negative independent life events experienced.

Dependent negative life events. Statistically significant associations of older age ($\chi^2_1 = 18.4$, $P < .001$), lower socioeconomic status ($\chi^2_1 = 5.2$, $P = .02$), and nonintact family ($\chi^2_1 = 8.3$, $P = .004$) with higher prevalence of negative dependent life events were found.

Uncertain negative life events. There were statistically significant effects for older age ($\chi^2_1 = 9.4$, $P = .002$) and lower socioeconomic status ($\chi^2_1 = 4.6$, $P = .03$) on the number of uncertain life events. By parents' report, there was also a significant effect for older age ($\chi^2_1 = 12.4$, $P < .001$) and

Table 3. Summary of NBRM Evaluating the Effects of Demographic Variables and Comorbidities (after adjusting for age, socioeconomic status, living situation, and race) on Negative Life Events Reported by Bipolar Youth

	Negative Life Events Variables, Estimate (SE)			
Variable	Total	Independent	Dependent	Uncertain
Demographic Variables[a]				
Age, y	0.04 (0.01)**	NS	0.07 (0.02)***	0.06 (0.02)**
Non-Caucasian race	0.22 (0.11)*	0.30 (0.14)*	NS	NS
Socioeconomic status	−0.12 (0.04)**	−0.14 (0.05)**	−0.10 (0.04)*	−0.11 (0.05)*
Nonintact family	0.29 (0.10)**	0.32 (0.12)**	0.31 (0.11)**	NS
Comorbidities[b]				
Anxiety disorder	NS[c]	NS[d]	NS	NS
ADHD	NS[e]	NS	0.21 (0.10)*	NS[f]
Conduct disorder	0.35 (0.13)**	0.32 (0.16)*	0.43 (0.13)***	NS
ODD	NS	NS	0.24 (0.10)**	NS

[a]Analyses were adjusted for all the other demographics, and included terms for sex and bipolar subtype, but these variables did not contribute significantly to explaining any of the life events variables.
[b]Analyses included terms for the effect of episode status, ADHD comorbidity, and substance abuse/dependence, but these terms did not contribute significantly to any of the models; table shows only results based on children report.
[c]Significant by parent report: 0.17 (0.08), $P \leq .05$.
[d]Significant by parent report: 0.27 (0.11), $P \leq .05$.
[e]Significant by parent report: 0.24 (0.08), $P \leq .01$.
[f]Significant by parent report: 0.26 (0.12), $P \leq .05$.
*$P \leq .05$.
**$P \leq .01$.
***$P \leq .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NBRM = negative binomial regression model, NS = not significant, ODD = oppositional defiant disorder.

living with a nonintact family ($\chi^2_1 = 4.3$, $P = .04$), but no effect was found for socioeconomic status ($\chi^2_1 = 0.2$, $P = .7$).

All of the following analyses were adjusted for age, socioeconomic status, living situation, and race. There were no differences in the number of negative life events (total, independent, dependent, or uncertain) among youth with bipolar I disorder, bipolar II disorder, and bipolar disorder NOS. Thus, the subsequent analyses were conducted after combining the 3 bipolar disorder subgroups.

Relationship between the number of negative life events and comorbid disorders. Multiple negative binomial regression models were built for each of the life events variables, by adding comorbid disorder variables as predictors to the models including age, socioeconomic status, living situation, and race, to see if these variables would further explain the responses. Interactions were checked and a final model was developed separately for each life event variable. Results are summarized in Table 3.

Total negative life events. Children with comorbid conduct disorder ($\chi^2_1 = 8.9$, $P = .003$) and oppositional defiant disorder (ODD) ($\chi^2_1 = 4.5$, $P = .03$) reported more total negative life events. In contrast, by parents' report, children with comorbid anxiety disorder ($\chi^2_1 = 5.25$, $P = .02$), ADHD ($\chi^2_1 = 8.7$, $P = .003$), and a trend for comorbid conduct disorder ($\chi^2_1 = 3.8$, $P = .05$) had more total negative life events.

Independent negative life events. By children's report, youth with comorbid conduct disorder ($\chi^2_1 = 4.2$, $P = .04$) and a trend for anxiety disorders ($\chi^2_1 = 3.4$, $P = .06$) showed a higher number of independent negative life events. By parents' report, children with comorbid anxiety disorders ($\chi^2_1 = 5.3$, $P = .02$) had an increased number of independent negative life events.

Dependent negative life events. Children with comorbid conduct disorder ($\chi^2_1 = 14.3$, $P < .001$) and ODD ($\chi^2_1 = 8.9$, $P = .003$) experienced more dependent negative life events, as reported by children. Parent reports showed similar associations with conduct disorder and ODD. In addition, parents reported that youth with ADHD experienced more dependent negative events ($\chi^2_1 = 4.1$, $P = .04$).

Uncertain negative life events. Specifically, youth with comorbid ADHD showed more negative uncertain life events per parent report ($\chi^2_1 = 4.3$, $P = .04$).

Life Events Among Bipolar Disorder, DEP-ANX, and Healthy Control Subjects

Negative life events. As shown in Table 4, the rates of negative life events (total, dependent, independent, and uncertain) for bipolar disorder subjects were not significantly different from those experienced by subjects with DEP-ANX disorders. However, both groups reported more negative life events (total, dependent, independent, and uncertain) than healthy controls (all P values $< .01$).

Similar results were found when only the most severe negative events were included in the analyses. There were no statistically significant differences between youth with bipolar disorder and those with DEP-ANX (1.2 ± 0.07 vs 1.6 ± 0.2, $\chi^2_1 = 2.5$, $P = .11$), but both groups reported significantly more severe life events than the healthy controls (0.7 ± 0.1) (all P values $< .01$).

Table 4. Prevalence of Negative and Positive Life Events for Bipolar Disorder, DEP-ANX, and Healthy Control Subjects[a]

Life Events	Bipolar Disorder (n = 387)	DEP-ANX (n = 65)	Healthy Controls (n = 64)	NBRM	*P* Value
Total, mean ± SE					
Negative	5.5 ± 0.3[b]	6.1 ± 0.5[b]	2.3 ± 0.2[c]	$\chi^2 = 48.2$	< .001
Positive	3.5 ± 0.2[b]	4.5 ± 0.5[c]	4.5 ± 0.3[c]	$\chi^2 = 10.0$	.007
Independent, mean ± SE					
Negative	2.2 ± 0.1[b]	2.8 ± 0.3[b]	1.0 ± 0.1[c]	$\chi^2 = 25.4$	< .001
Positive	1.1 ± 0.2	1.0 ± 0.2	0.8 ± 0.1	$\chi^2 = 2.5$	.3
Dependent, mean ± SE					
Negative	2.2 ± 0.1[b]	2.2 ± 0.2[b]	0.6 ± 0.1[c]	$\chi^2 = 44.1$	< .001
Positive	1.8 ± 0.1[b]	2.8 ± 0.2[c]	3.1 ± 0.2[c]	$\chi^2 = 27.9$	< .001
Uncertain, mean ± SE					
Negative	1.1 ± 0.1[b]	1.2 ± 0.1[b]	0.7 ± 0.1[c]	$\chi^2 = 9.9$	.007
Positive	0.6 ± 0.0	0.8 ± 0.1	0.5 ± 0.1	$\chi^2 = 3.6$	.2

[a]Analyses are controlled for age, sex, and race.
[b,c]Means with different superscripts are significantly different, with *P* values ≤ .05.
Abbreviations: DEP-ANX = depressive and/or anxiety disorder, NBRM = negative binomial regression model.

Positive life events. Youth with bipolar disorder experienced fewer total and dependent positive life events than youth with DEP-ANX and healthy controls (all *P* values < .01). There were no between-group differences in the number of independent and uncertain life events (Table 4).

DISCUSSION

To our knowledge, this is the largest study to systematically examine negative life events among children and adolescents with bipolar spectrum disorders and the first to analyze life events taking into account the effects of important factors such as bipolar subtype, comorbid disorders, and demographic characteristics.

Our results indicate that demographics factors such as older age, lower socioeconomic status, living with nonintact family, and non-Caucasian race significantly correlated with the number of total negative life events. Specifically, higher frequency of independent negative life events was associated with lower socioeconomic status, nonintact family, and non-Caucasian race; higher rates of dependent and uncertain negative life events were associated with older age, lower socioeconomic status, and nonintact family. There were no effects for sex or different bipolar disorder subgroups in the number of reported negative life events (independent, dependent, and uncertain).

Overall, as reported collectively by youth and their parents, bipolar youth with comorbid ADHD, ODD, conduct disorder, and anxiety disorders showed more total negative life events. Specifically, subjects with comorbid conduct disorder and anxiety disorder showed more independent negative life events, whereas subjects with comorbid conduct disorder, ODD, and ADHD reported more dependent negative life events.

Youth with bipolar disorder and youth with DEP-ANX reported similar rates of negative life events (total, independent, dependent, and uncertain), and both groups had more negative life events when compared to the healthy controls. Similar results were found when the analysis was restricted to only the most severe negative life events. However, youth with bipolar disorder reported fewer total and dependent positive life events than youth with DEP-ANX or healthy controls.

Before discussing the above results in detail, it is important to take into account the limitations of this study. First, this is a cross-sectional study, and life events and symptoms were retrospectively ascertained. We are prospectively following the entire sample, which will allow a more precise evaluation of the relation between life events and clinical outcome in bipolar youth. Second, life events were ascertained with the LEC and not more precise methods to evaluate life events such as the Life Events Difficulties Schedule.[37,38] The LEC contains only a limited number of life events; therefore other life events not listed in the checklist may have occurred and not been counted. Moreover, interview methods to assess life events more accurately classify events as dependent or independent and the subjective versus objective threat severity of a given life event compared with checklists.[24] Although interview methods may provide greater detail and therefore greater certainty regarding the classification of life events,[24] the LEC provides a reliable estimate of the overall stress level and is feasible to use in large samples.[23] Lastly, information regarding the rates of comorbid disorders in a subgroup of the subjects (eg, ADHD) among the historical DEP-ANX group was not available.

Similar to our findings, older age, low socioeconomic status, nonintact family, and non-Caucasian race have been found in the literature to be associated with an increased number of life events.[39–41] Specifically, studies have found that there is a developmentally normative increase in the number of negative life events after puberty regardless of sex.[42] Prior research suggests that these increases in the number of negative life events during adolescence is more specific for dependent life events.[43] Similarly to Kim and

colleagues,[21] we found that older age is related to an increase in negative *dependent* life events, but there was no effect on the number of *independent* life events.

Similar to that found by Mayer and colleagues,[6] we did not find sex differences in the number of negative life events (independent or dependent) in our clinical sample. However, it should be noted that prior findings in this area have been mixed. Some studies have suggested that stress generation (negative dependent life events) may be more evident in female subjects than in male subjects.[8,44–46] Yet, a recent study with at-risk adolescents[47] found that boys experienced higher levels of dependent life events compared to girls. A third study found that the overall number of dependent stressors was similar across boys and girls, but they showed different patterns of stress generation.[43]

Although there are similarities between the phenomenology of bipolar disorder among youth and adults, there are some developmental differences such as higher rates of recurrences, more frequent changes in symptom status and polarity, more mixed/cycling episodes, and high rates of comorbid disorders, especially externalizing and internalizing disorders.[26] These factors are important considerations when studying life events in bipolar youth.[48] Our results indicate that comorbid disorders such as ADHD, ODD, conduct disorder, and anxiety disorders are significantly associated with increased number of negative life events in youth with bipolar disorder. It seems that externalizing comorbid disorders are more highly correlated with dependent life events whereas internalizing comorbid disorders are more related to independent life events. Rucklidge[19] has previously suggested that there is an association among bipolar youth between negative life events, external locus of control, and propensity to act out when angry. Additionally, studies of adolescents with unipolar depression have shown that those with comorbid externalizing disorder demonstrate higher rates of dependent episodic stressful life events.[49]

Bipolar youth and DEP-ANX youth were exposed to more negative life events (independent and dependent) in the year prior to baseline assessment than healthy controls. These results are consistent with those reported in the adult[3,4] and pediatric depression[7,8] and bipolar disorder[18,19] literature. Similarly, prior research also suggests that children with bipolar disorder appear to have more independent and dependent negative life events than children with ADHD.[18]

Contrary to our hypothesis, in this study youth with bipolar disorder and youth with DEP-ANX had similar rates of negative life events (independent, dependent, and uncertain) and severe negative life events. This last result may be accounted by the fact that both mood groups were recruited at university centers where more severe cases are referred. Alternatively, these results suggest that mood disorders as a continuum may share a similar mechanism of environment (stressful life events) and genetic interactions as well as stress generation (dependent life events) tendency.[50] In this way and despite methodological limitations, studies in offspring of bipolar disorder subjects have shown that increased exposure to negative life events is associated with more psychopathology (especially mood disorders).[16,51–53] Interestingly, even without Axis I disorders, higher levels of anxiety and depression mediated the relationship between negative dependent life events and onset of a mood disorder, suggesting that prodromic psychopathology may account for the generation of stressful life events.[16,51]

On the other hand, after controlling for age, bipolar youth reported fewer positive life events (total and dependent) than DEP-ANX and healthy youth. This result may be interpreted as bipolar youth having less ability to generate positive life events or a propensity to perceive life events as negative instead of positive as compared with DEP-ANX or healthy youth. Youth with DEP-ANX showed similar rates of total and dependent positive life events to healthy controls, which may counteract in some way the increasing number of negative life events in youth with DEP-ANX.

Among the possible explanations of youth with bipolar disorder reporting fewer positive total and dependent life events may be a limited social support or less cohesive family environments.[54–56] Since positive life events may increase the probability of remission in nonpsychotic disorder,[57] one of the main goals in psychotherapy for bipolar youth should be to improve the child's reappraisal of the experienced life events. Additionally, enhancing factors such family support, mood regulation, and cognitive and behavioral skills on family and individual therapy may increase the rates of total and dependent positive life events in these youth.[58]

In summary, our results suggest that in addition to being at high risk for physical and sexual abuse,[22] children and adolescents with bipolar spectrum disorders are also exposed to many other negative independent and dependent life events, especially those youth with comorbid disorders. Whether dependent or independent of the child's behavior, exposure to negative events may worsen the symptoms of the bipolar disorder, the psychosocial impact of bipolar disorder, and the symptoms of other comorbid disorders.[3] Therefore, it is important to identify this illness early and to prevent the onset and/or ameliorate the ongoing negative events to which the child is exposed using state-of-the-art psychosocial and pharmacologic treatments.[59–64] Finally, longitudinal analyses of this sample are also needed to clarify the role of life events in the course and outcome of the illness. For example, it will be important to determine whether negative life events predict any mood episodes and/or type (depressive, manic) of mood episode.

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