

# Predictors of Prospectively Examined Suicide Attempts Among Youth With Bipolar Disorder

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**Context:** Individuals with early onset of bipolar disorder are at high risk for suicide. Yet, no study to date has examined factors associated with prospective risk for suicide attempts among youth with bipolar disorder.

**Objective:** To examine past, intake, and follow-up predictors of prospectively observed suicide attempts among youth with bipolar disorder.

**Design:** We interviewed subjects, on average, every 9 months over a mean of 5 years using the Longitudinal Interval Follow-up Evaluation.

**Setting:** Outpatient and inpatient units at 3 university centers.

**Participants:** A total of 413 youths (mean [SD] age, 12.6 [3.3] years) who received a diagnosis of bipolar I disorder (n=244), bipolar II disorder (n=28), or bipolar disorder not otherwise specified (n=141).

**Main Outcome Measures:** Suicide attempt over prospective follow-up and past, intake, and follow-up predictors of suicide attempts.

**Results:** Of the 413 youths with bipolar disorder, 76 (18%) made at least 1 suicide attempt within 5 years of

study intake; of these, 31 (8% of the entire sample and 41% of attempters) made multiple attempts. Girls had higher rates of attempts than did boys, but rates were similar for bipolar subtypes. The most potent past and intake predictors of prospectively examined suicide attempts included severity of depressive episode at study intake and family history of depression. Follow-up data were aggregated over 8-week intervals; greater number of weeks spent with threshold depression, substance use disorder, and mixed mood symptoms and greater number of weeks spent receiving outpatient psychosocial services in the preceding 8-week period predicted greater likelihood of a suicide attempt.

**Conclusions:** Early-onset bipolar disorder is associated with high rates of suicide attempts. Factors such as intake depressive severity and family history of depression should be considered in the assessment of suicide risk among youth with bipolar disorder. Persistent depression, mixed presentations, and active substance use disorder signal imminent risk for suicidal behavior in this population.

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**B**IPOLAR DISORDER CONFERS A substantially high risk for completed suicide, among the highest of all psychiatric disorders.<sup>1</sup> Among adults with bipolar disorder, 25% to 50% make at least 1 suicide attempt in their lifetime, and 8% to 19% will die of suicide.<sup>2</sup>

Given these sobering statistics, studies seek to identify demographic, clinical, and family history factors associated with prospective risk for suicide attempt among adults with bipolar disorder<sup>1</sup> to identify targets for intervention and prevention. Such studies<sup>2-5</sup> primarily examine whether past and/or present factors, assessed at study intake, reliably predict a

suicide attempt during longitudinal follow-up. Studies using this approach have identified clinical factors predictive of prospective risk for a suicide attempt in adults with bipolar disorder, including a history of attempt,<sup>2,6-9</sup> time spent in a depressed and/or mixed episode in the preceding year,<sup>2,10</sup> feelings of hopelessness<sup>4,11</sup> and hostility,<sup>11</sup> and severity of depressive episode at study intake.<sup>7</sup> In addition, comorbid panic disorder, substance use disorder,<sup>8</sup> and cigarette smoking<sup>7</sup> at study intake predict suicidal behavior during longitudinal follow-up among adults with bipolar disorder. In keeping with the literature on the familial transmission of suicidal behavior in general,<sup>12,13</sup> a family history of

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attempted or completed suicide is also a reliable predictor of prospective suicide attempt among adults with bipolar disorder.<sup>8,11</sup> These findings provide important information about factors that predispose adults with bipolar disorder to suicidal behavior.<sup>14</sup> To further enhance suicide prevention efforts, the American Association of Suicidology underscored the need for studies examining proximal risk factors for suicide (ie, those occurring in close temporal relationship and thus conferring near-term risk).<sup>15</sup> Yet, only 3 prospective studies<sup>2,10,16</sup> to date examine proximal risk factors for suicide attempts in adults with bipolar disorder, and, to our knowledge, there are no studies that have examined proximal risk factors for suicide attempts among youth with bipolar disorder.

The only demographic factor significantly associated with prospective risk for suicidal behavior in the literature on adults with bipolar disorder is younger age at study intake.<sup>4,11</sup> Up to 65% of adults with bipolar disorder experience the onset of the disorder before adulthood,<sup>3,4</sup> and those adults with an early onset of illness are at higher risk for suicidal behavior.<sup>4,5,17-19</sup> Studies<sup>20-23</sup> report a lifetime suicide attempt rate of 20% to 47% among youth with bipolar disorder, and psychological autopsy studies indicate that, of all psychiatric diagnoses, bipolar disorder imparts the greatest risk for completed suicide among youth.<sup>24</sup> However, to date, no prospective study has examined specific risk factors (whether assessed in the past, at study intake, or during longitudinal follow-up) for suicide attempts among youth with bipolar disorder.

In a cross-sectional analysis using retrospective data gathered at study intake, our group previously documented high rates (33%) of lifetime history of suicide attempt in a large, well-characterized sample of youth with bipolar disorder from the Course and Outcome of Bipolar Youth (COBY) study,<sup>21</sup> which was funded by the National Institute of Mental Health (NIMH). The analysis indicated that the most robust past history factors associated with history of suicide attempt among youth with bipolar disorder were histories of mixed episodes, psychosis, hospitalization, nonsuicidal self-injurious behavior, panic disorder, and substance use disorder. To date, we have followed 413 youths with bipolar disorder enrolled in the COBY study for an average of 5 years. In this sample, we thus aimed to (1) document the rate and nature of prospectively examined suicide attempts among youth with bipolar disorder; (2) examine the relationship between past and intake demographic, clinical, and family history variables and prospectively examined suicide attempts; and (3) conduct the first-ever examination of the relationship between time-varying risk factors during follow-up and prospectively examined suicide attempts. The identification of such risk factors may inform the development of both preventive and therapeutic interventions for this high-risk group.

## METHODS

Please refer to prior articles<sup>25,26</sup> for a detailed description of the methods used in the COBY study. We briefly summarize the study method.

## PARTICIPANTS

Study participants were recruited from outpatient clinics, inpatient units, advertisements, and clinical referrals during the period from October 2000 through July 2006 at 3 sites: the University of California, Los Angeles, Brown University, and the University of Pittsburgh. The sample includes 446 youths recruited at the ages of 7 to 17 years 11 months who gave informed consent to participate in a longitudinal study evaluating their illness. All participants had a primary diagnosis of *DSM-IV* bipolar I disorder or bipolar II disorder or met operationally defined criteria for bipolar disorder not otherwise specified (see below and Axelson et al<sup>27</sup>). Youths with schizophrenia, mental retardation, autism, or mood disorders secondary to substances, medications, or medical illness were excluded. The present analyses include 413 subjects who completed at least 1 follow-up assessment (mean length of follow-up, 261.7 weeks; range, 26.0-439.0 weeks); longitudinal data were assessed retrospectively at a mean (SD) follow-up period of 37.0 (20.4) weeks. The mean (SD) age of the participants at study intake was 12.6 (3.3) years; 53% of the participants were male, and the majority (82%) were white. More information on clinical course and outcomes among COBY youth can be found in Birmaher et al.<sup>26</sup>

## PROCEDURES

Each participating site obtained institutional review board approval for all study procedures. Research staff trained to acceptable levels of reliability on study evaluations<sup>26</sup> conducted the assessments. We obtained consent from parents and youths prior to administration of study procedures.

### Psychiatric Diagnosis

Study clinicians assessed participants' present and past psychiatric diagnoses at study intake via direct interviews with parents and children. Nonmood psychiatric disorders were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Version (K-SADS-PL),<sup>28</sup> and mood symptoms were assessed by the mood disorder sections of the K-SADS—Present Episode, 4th revision (K-SADS-P),<sup>29</sup> plus additional items from the K-SADS—Mania Rating Scale (K-SADS-MRS).<sup>30</sup> All participants met *DSM-IV* criteria for bipolar disorder (244 participants with bipolar I disorder, 28 participants with bipolar II disorder, and 141 participants with bipolar disorder not otherwise specified). We used criteria operationalized for the COBY study to diagnose bipolar disorder not otherwise specified.<sup>25,27</sup>

### Past and Intake Factors

We obtained demographic information via a parent-report form; data on history of treatment and history of abuse were obtained using a medical history questionnaire. Socioeconomic status was ascertained using the Hollingshead Four Factor Index of Social Status.<sup>31</sup> The subject's primary caretaker was interviewed at study intake about his or her personal psychiatric history using the Structured Clinical Interview for *DSM-IV*<sup>32</sup> and about the psychiatric status of other first- and second-degree relatives using an enhanced version of the Family History Screen.<sup>33</sup> Past and current cigarette smoking and alcohol use were ascertained via the K-SADS-PL. Repeated alcohol use was considered positive if the subject endorsed at least 4 weeks (which may be nonconsecutive) during which he or she consumed at least 2 alcoholic beverages. We assessed family conflict via the child- and parent-report versions of the Conflict

Behavior Questionnaire<sup>34</sup> and family environment via the child- and parent-report versions of the Family Adaptability and Cohesion Evaluation Scales–II.<sup>35</sup> Participants reported life events over the prior year using the Life Events Checklist.<sup>36</sup> Global functioning (both current functioning and most severe functioning in the past) was assessed using the Children's Global Assessment Scale.<sup>37</sup> Severity of depressive and manic symptoms for the current affective episode (worst week in the month preceding assessment) and worst past episode were recorded on the K-SADS-P depression section and the K-SADS-MRS, respectively. So as not to confound the analyses examining the relationship between severity of depressive symptoms on the K-SADS-P and suicidality, the total K-SADS-P depressive severity scores presented exclude the K-SADS-P suicidal ideation item.

A past or present suicide attempt was defined as any self-injurious act that reached or exceeded an operationalized threshold of lethal intent and/or medical lethality, as assessed via the K-SADS-P depression section suicidal acts items (assessed during the current episode and during the most severe past episodes) and/or the K-SADS Summary Lifetime Diagnostic Checklist suicide attempt item.<sup>21</sup> Past or current suicidal ideation were considered positive if K-SADS-P depression summary scores reflected past or current suicidal ideation rated "3" (mild) or greater. Past or current nonsuicidal self-injurious behavior was assessed via the K-SADS-P nonsuicidal self-damaging acts item and was considered positive if rated "3" (infrequent) or greater.

### Follow-up Factors

Symptoms and diagnoses since the prior follow-up were assessed using the Longitudinal Interval Follow-up Evaluation (LIFE).<sup>38</sup> Week-by-week severity ratings that correspond to *DSM-IV* criteria were documented on the LIFE Psychiatric Status Rating (PSR)<sup>39</sup> scales based on consensus scores from interviews with parents and their children. Mood disorders are rated on the PSR using a 1 to 6 rating scale (with 1 signifying no symptoms, 2-4 signifying subthreshold *DSM-IV* symptoms, and 5-6 signifying full-threshold *DSM-IV* criteria). For the follow-up analyses, mixed states were operationalized as either a threshold (ie, 5/6) rating for both depression and mania during the same follow-up week or a threshold rating for depression, mania, or hypomania combined with a subthreshold rating<sup>2,4</sup> on the opposite mood pole. Medication exposure during follow-up was assessed using the Psychotropic Treatment Record of the LIFE, and psychosocial treatment exposure was assessed using the LIFE Psychosocial Treatment Schedule. Ratings account for reported adherence (medication) and attendance (psychosocial treatment).

### Prospectively Examined Suicide Attempts

Suicide attempts during follow-up were ascertained using the LIFE method to create a LIFE Self-Injurious/Suicidal Behavior Scale. Clinicians record all self-injurious behaviors, regardless of intent, that occurred during the follow-up period on a week-by-week basis. For each behavior, ratings of intent to die and medical threat were assigned per the K-SADS-P Depression Scale ratings for these items,<sup>29</sup> with intent on a 1 (none) to 6 (extreme, careful planning, and every expectation of death) scale and with lethality on a 1 (no danger) to 7 (death) scale. In addition, the clinician coded the method used (eg, overdose or hanging), the date, and the subject's clinical condition at the time of the behavior (eg, intoxicated or psychotic). According to the definitional system proposed by O'Carroll and colleagues, a suicide attempt is "a potentially self-injurious behavior with a nonfatal outcome for which there is evidence

(either explicit or implicit) that the person intended at some level to kill himself/herself. A suicide attempt may not result in injuries."<sup>40(p247)</sup> To capture the core elements of this definition (intent and/or lethality), as well as to decrease the likelihood that nonsuicidal self-harm behaviors would be classified as suicide attempts, any self-injurious behavior that included definite intent (intent score of 3, definite but ambivalent, or greater) and/or mild lethality (medical threat score of 3, mild, or greater) was considered a suicide attempt. This is in keeping with our prior work examining correlates of lifetime suicidal behavior and nonsuicidal self-injury in this sample.<sup>21,41</sup> The COBY clinicians reviewed more than 65% of follow-up assessments with a study investigator to achieve consensus ratings. To date, there have been no completed suicides in the sample.

## STATISTICAL ANALYSIS

### Past and Intake Factors Associated With Prospectively Examined Suicide Attempts

We screened past and intake risk factors for their association with prospectively examined suicide attempts by using log-rank tests for categorical variables and Cox proportional hazards regression for continuous variables. Factors associated with prospectively examined suicide attempts in the univariate analyses ( $P < .10$ ) were then entered into a stepwise Cox proportional hazards regression model, controlling for significant demographic variables from the univariate analyses. Test and graphical diagnostics for proportional hazards support the assumptions of the model. We applied the Benjamini-Hochberg step-up procedure post hoc to all univariate analyses to control for the false discovery rate. When univariate factors were selected for the multivariate Cox proportional hazards regression model based on these adjusted  $P$  values ( $P < .10$ ), the results from the multivariate model remained the same. We therefore report unadjusted  $P$  values.

### Follow-up Factors Associated With Prospectively Examined Suicide Attempts

To identify time-varying factors during follow-up that were associated with prospective risk for suicide attempt, we used Cox proportional hazards regression with time-varying covariates. Data for time-varying covariates were ascertained using the LIFE. Weekly values on the PSR for symptom severity and treatment exposure were aggregated over 8-week intervals in 2 ways: (1) percentage of weeks during the 8-week follow-up period during which the factor was present (eg, percentage of weeks during which the participant met full-threshold criteria for depression) and (2) maximum PSR severity score, ranging from 1 (asymptomatic) to 6 (full threshold with substantial severity and impairment), during the 8-week period. Given that this is the first prospective analysis of time-varying risk factors associated with suicidal behavior in youth with bipolar disorder, we had limited information to inform our decision regarding a preferred prospective time period for analysis. We selected 8-week follow-up intervals because this reflects a plausible window during which clinical, psychosocial, and biological factors potentially associated with suicidal behavior may be exerting their effects. We conducted a sensitivity analysis to determine the differential effects of examining 4- and 12-week follow-up intervals, and we found similar results.

Among those youth who exhibited a prospectively examined suicide attempt, the 8-week interval prior to the attempt was examined separately from the other 8-week follow-up intervals. Follow-up intervals for attempters were defined in

8-week blocks working backward from the suicide attempt. For subjects with multiple attempts, data were censored at the first attempt during follow-up. Regression analyses examined whether each covariate is temporally associated with risk for a prospectively examined suicide attempt by comparing its value during the 8-week period prior to the attempt with its values measured during 8-week periods earlier in the course of follow-up for the attempters and over the mean of all 8-week periods during follow-up for the nonattempters. We first performed univariate analyses of these factors; those with a significance of  $P < .10$  were entered into a stepwise multivariate Cox regression analysis, controlling for significant demographic variables from the univariate analyses. Hazard ratios (HRs) and 95% CIs were computed. All  $P$  values are based on 2-tailed tests with  $\alpha = .05$ .

### Interpreting the HRs

Hazard ratios for PSR analyses examining covariates measured in percentage of weeks (0%-100% scale) are interpreted as the increased risk for a suicide attempt associated with each 1% increase in the amount of the 8-week period during which the covariate was present. To illustrate, the HR for full-threshold depression is 1.02. Therefore, a 1% increase in percentage of an 8-week period with full-threshold depression is associated with a 2% increased risk for a suicide attempt. To calculate the increased risk for a suicide attempt associated with a  $k$ -unit increase in the percentage of weeks during which the covariate was present, raise the HR to the  $k$ -power.<sup>42</sup> Therefore, the increase in suicide risk for an individual who went from 25% of an 8-week follow-up period with full-threshold depression (ie, 2 out of 8 weeks) to 50% of the next 8-week follow-up period with full-threshold depression (ie, 4 of 8 weeks of the 8-week period; a 25-unit increase) is 64% ( $1.02^{25} = 1.64$ ). Hazard ratios for maximum PSR analyses (1-6 scale) are interpreted as the increased risk for a suicide attempt associated with each 1-unit increase in maximum PSR score during the 8-week period. For example, the HR for maximum severity of depression PSR score is 2.49. This means that a 1-unit increase from a maximum PSR score of 2 to 3 from one 8-week period to another is associated with a 149% increase in suicide risk. Risk associated with  $k$ -unit change is similarly calculated using the equation presented in this paragraph ( $HR^k$ ).

## RESULTS

### PROSPECTIVELY EXAMINED SUICIDE ATTEMPTS

Of the 413 subjects, 76 (18%) attempted suicide once or more during follow-up; of the 76 subjects who attempted suicide, 31 attempted suicide more than once (mean [SD] number of attempts per attempter, 2.1 [2.9]), for a total of 163 suicide attempts in the sample to date.

The evaluator rated the clinical and psychosocial conditions surrounding all prospectively examined suicide attempts; we collected independent ratings on these conditions for every attempt during follow-up (including multiple attempts by the same individual) because different attempts by the same subject were not presumed to involve similar clinical and psychosocial circumstances. These ratings indicate that 94 of 163 attempts (58%) were made when subjects reported they were taking prescribed psychotropic medication. Subjects reported that, prior to the suicide attempt, they communicated with others regarding their intent to attempt suicide in 69 (42%)

of these attempts. Of the 163 attempts, only 4 (2%) were reportedly associated with psychotic symptoms, and 8 (5%) were committed when intoxicated. Of the 163 attempts during follow-up, 51 (31%) were preceded by a significant life event per the subject's report; the 2 most commonly reported categories of events included discord in or breakup of a romantic relationship (9 attempts [6%]) and family conflict (8 attempts [5%]).

### PAST AND INTAKE FACTORS ASSOCIATED WITH PROSPECTIVELY EXAMINED SUICIDE ATTEMPTS

#### Univariate Analyses

**Table 1** presents univariate analyses comparing past and intake demographic and clinical variables between those youths who attempted suicide during follow-up with those who did not. Suicide attempters were more likely to be female. With respect to past clinical variables, attempters had greater rates of past psychiatric hospitalization, nonsuicidal self-injurious behavior, and both suicidal ideation and attempt. Most severe past ratings of global functioning (using the Children's Global Assessment Scale) were worse among attempters; attempters also exhibited greater depressive and manic severity at study intake (using the depression section of the K-SADS-P and using the K-SADS-MRS). Bipolar disorder subtype did not distinguish attempters from nonattempters. The only category of lifetime comorbid Axis I disorders that differentiated attempters from nonattempters was substance use disorder, with attempters exhibiting greater rates. Youths who attempted suicide during follow-up were more likely to have past exposure to an antidepressant. Finally, depression and suicidal behavior were more common among the first- and second-degree relatives of suicide attempters.

#### Multivariate Model

A Cox proportional hazards regression model controlling for sex indicated that depressive severity (using the depression section of the K-SADS-P; HR, 1.03 [95% CI, 1.01-1.06];  $P = .01$ ) and family history of depression (HR, 3.8 [95% CI, 1.19-12.16];  $P = .02$ ) were significantly associated with an increased risk of a prospectively examined suicide attempt.

### FOLLOW-UP FACTORS ASSOCIATED WITH PROSPECTIVELY EXAMINED SUICIDE ATTEMPTS

#### Univariate Analyses

Univariate analyses comparing time-varying follow-up factors aggregated over 8-week intervals between those youths who exhibited a prospectively examined suicide attempt with those who did not are presented in **Table 2**. Greater risk for a prospective suicide attempt was associated with greater percentage of time in the preceding 8 weeks meeting full-threshold criteria for any mood episode: specifically, a greater percentage of time meeting threshold criteria for depression and mixed states, but

**Table 1. Past and Intake Factors Associated With Prospectively Examined Suicide Attempts**

Characteristic	Youth		Statistics	
	No Suicide Attempt During Follow-up (n = 337)	Suicide Attempt During Follow-up (n = 76)	$\chi^2$ or <i>t</i> Value	<i>P</i> Value
<b>Demographics</b>				
Age, mean (SD), y	12.5 (3.2)	13.1 (3.3)	1.49	.22
SES score, mean (SD)	3.4 (1.2)	3.4 (1.2)	0.05	.83
White, %	82.2	81.6	0.29	.59
Male, %	56.1	42.1	4.98	.03
Living with both natural parents, %	42.7	39.5	0.20	.66
<b>Present clinical factors</b>				
Bipolar disorder subtype, %				
I	59.7	56.6	0.44	.80
II	6.2	9.2		
NOS	34.1	34.2		
C-GAS score, mean (SD)				
Most severe past rating	38.2 (10.5)	34.3 (10.5)	6.80	.009
Present rating	55.2 (12.3)	52.7 (11.9)	3.08	.08
Dep-P score, mean (SD)				
Most severe past rating	17.4 (11.5)	19.1 (12.0)	1.37	.24
Present rating	12.7 (9.2)	18.7 (9.7)	19.8	<.001
MRS score, mean (SD)				
Most severe past rating	34.0 (8.3)	34.7 (6.9)	0.54	.46
Present rating	22.0 (12.2)	26.5 (11.0)	6.48	.01
<b>Lifetime comorbid diagnoses, %</b>				
ADHD	60.8	52.6	1.47	.23
Conduct disorder	12.2	10.5	0.18	.67
ODD	40.4	32.9	2.05	.15
Substance use disorder	7.1	14.5	4.23	.04
Any anxiety disorder	37.4	47.4	1.96	.16
Panic disorder	5.3	5.3	0.05	.83
<b>Past clinical factors, %</b>				
Psychiatric hospitalization	48.5	67.1	5.58	.02
Nonsuicidal self-injury	34.6	50.0	6.33	.01
Suicidal ideation	72.1	88.2	8.32	.004
Suicide attempt	26.1	44.7	10.12	.002
Mixed state	25.8	31.6	1.80	.18
Psychosis	21.7	25.0	0.31	.58
Physical or sexual abuse	18.4	25.0	1.21	.27
Lifetime cigarette smoking	23.0	33.3	2.70	.10
Lifetime excessive drinking	7.9	15.9	3.41	.07
<b>Family functioning at study intake</b>				
FACES-II score, mean (SD)				
Cohesion				
Child rated	55.8 (13.2)	56.4 (11.7)	0.24	.62
Parent rated	59.8 (11.2)	58.9 (10.7)	0.05	.82
Adaptability				
Child rated	43.8 (9.3)	44.7 (8.2)	0.63	.43
Parent rated	45.3 (7.1)	46.6 (7.2)	2.11	.15
Family conflict CBQ score, mean (SD)				
Child rated	8.5 (5.8)	7.9 (5.7)	0.95	.33
Parent rated	11.5 (5.8)	10.9 (5.4)	0.45	.50

(continued)

not mania/hypomania. Greater percentage of time with psychotic symptoms in the context of mood episodes in the preceding 8 weeks was also associated with greater prospective risk for a suicide attempt. With respect to comorbid Axis I conditions, greater number of weeks spent meeting criteria for any comorbid disorder (specifically, panic and substance use disorders) in the preceding 8 weeks confer an elevated prospective risk for a suicide attempt. Pharmacotherapy regimen, which included taking any psychotropic medication, as well as

taking an antidepressant medication, in the preceding 8-week period was not associated with risk for attempt. However, greater risk was predicted for subjects with greater exposure (percentage of weeks) to any psychosocial treatment, and also, specifically, to inpatient/residential and outpatient psychosocial services, in the preceding 8 weeks.

More severe maximum LIFE PSR ratings for both depression and mania/hypomania during the preceding 8 weeks were also strongly associated with prospective risk

**Table 1. Past and Intake Factors Associated With Prospectively Examined Suicide Attempts (continued)**

Characteristic	Youth		Statistics	
	No Suicide Attempt During Follow-up (n = 337)	Suicide Attempt During Follow-up (n = 76)	$\chi^2$ or <i>t</i> Value	<i>P</i> Value
Life events (past year)				
LEC score, mean (SD)				
Negative events				
Child rated	5.2 (4.9)	5.8 (5.3)	0.66	.42
Parent rated	4.6 (3.7)	5.7 (3.9)	3.63	.06
Positive events				
Child rated	3.4 (3.9)	3.3 (2.5)	0.08	.77
Parent rated	2.5 (2.9)	2.8 (1.8)	0.80	.37
Past medication use, %				
Any psychotropic medication	95.6	96.1	0.01	.92
Antimanic	80.4	85.5	0.65	.42
Antidepressant	51.0	75.0	10.58	.001
Stimulant	57.3	51.3	0.81	.37
Present medication use, %				
Any psychotropic medication	89.6	86.8	0.95	.33
Antimanic	71.2	75.0	0.22	.64
Antidepressant	26.4	34.2	1.03	.31
Stimulant	28.8	19.7	3.14	.08
Family history (1st- or 2nd-degree relatives), %				
Depression	79.2	94.7	9.33	.002
Mania/hypomania	49.3	57.9	1.42	.23
ADHD	38.0	46.1	2.20	.14
Conduct disorder	32.1	39.5	2.12	.15
Anxiety disorder	62.3	72.4	1.93	.17
Substance use disorder	68.3	72.4	0.90	.34
Suicide attempt	38.6	50.0	4.19	.04

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; C-GAS, Children's Global Assessment Scale; CBQ, Conflict Behavior Questionnaire; Dep-P, depression section of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present Episode, 4th revision (suicidal ideation item excluded from total); FACES-II, Family Adaptability and Cohesion Scale—II; LEC, Life Events Checklist; MRS, Mania Rating Scale of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children; NOS, not otherwise specified; ODD, oppositional defiant disorder; SES, socioeconomic status.

for a suicide attempt. Maximum LIFE PSR depression and mania/hypomania ratings were highly correlated with percentage of follow-up weeks spent with full-threshold depression ( $r=0.62$ ) and mania/hypomania ( $r=0.45$ ), respectively. We therefore omitted maximum LIFE PSR depression and mania/hypomania from the multivariate model.

### Multivariate Model

Using Cox proportional hazards regression with time-varying covariates controlling for sex, we identified greater risk for a prospectively examined suicide attempt associated with the following factors in the preceding 8-week follow-up period: more weeks spent with depression (HR, 1.02 [95% CI, 1.01-1.03];  $P < .001$ ), mixed symptoms (HR, 1.01 [95% CI, 1.0-1.02];  $P = .05$ ), and substance use disorder (HR, 1.01 [95% CI, 1.01-1.02];  $P < .001$ ) and more weeks receiving outpatient psychosocial services (HR, 1.01 [95% CI, 1.00-1.01];  $P = .02$ ).

### COMMENT

To our knowledge, this is the first study to examine past, intake, and time-varying follow-up predictors of prospectively examined suicide attempts among youth with bipolar disorder. Even in the literature on adult bipolar

disorder, data on near-term factors associated with prospective suicide risk are limited. Our findings provide further evidence of the substantial risk for suicidal behavior associated with early-onset bipolar disorder: 18% of youth with bipolar disorder made at least 1 clinically significant suicide attempt within 5 years of study intake, and 8% made multiple attempts. Attempt rates were similar among youth with bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified. The most potent past and intake factors predictive of a prospectively examined suicide attempt included severity of depressive episode at study intake and family history of depression. More weeks spent with threshold depression, substance use disorder, and mixed mood symptoms, as well as more weeks receiving outpatient psychosocial services in the preceding 8-week period, predicted greater likelihood of a prospective suicide attempt. Therefore, family history, severity of depressive episode at study intake, and near-term persistence of depression, mixed states, and substance use disorder independently contribute to the prediction of prospective suicidal behavior among youth with bipolar disorder.

The 18% rate of suicidal behavior over an average of 5 years of follow-up that we report is similar to that documented in other prospectively observed samples of youth with bipolar disorder. Strober and colleagues<sup>22</sup> reported medically significant suicide attempts in 20% of adoles-

**Table 2. Follow-up Factors Associated With Prospective Risk for a Suicide Attempt**

Factor	Mean (SD)			Statistics		
	Suicide Attempt During Follow-up (n = 74)		No Suicide Attempt During Follow-up (n = 337)	$\chi^2$ Value	P Value	Hazard Ratio
	8-wk Period Prior to Attempt	8-wk Period During Follow-up				
Mood state, <sup>a</sup> % of wk						
Any subthreshold mood state	41.2 (39.1)	38.7 (27.5)	39.4 (26.5)	0.12	.73	
Full-threshold depression	20.1 (33.5)	11.2 (17.6)	4.4 (9.2)	39.29	<.001	1.021
Full-threshold mania/hypomania	3.0 (13.2)	3.8 (9.3)	2.8 (6.7)	0.11	.74	
Mixed mood state	15.4 (27.6)	13.5 (19.0)	6.2 (12.5)	10.81	.001	1.012
Any full-threshold mood state	38.5 (32.8)	28.5 (27.4)	13.4 (18.0)	38.91	<.001	1.017
Any mood state with psychosis	6.8 (22.9)	3.6 (14.9)	2.1 (8.5)	6.46	.01	1.012
Maximum severity, <sup>b</sup> A-LIFE PSR score						
Depression	4.4 (1.3)	3.4 (1.0)	2.6 (0.9)	76.64	<.001	2.493
Mania/hypomania	3.0 (1.5)	2.9 (1.1)	2.5 (0.9)	8.83	.003	1.76
Comorbid disorders, <sup>a</sup> % of wk meeting full-diagnostic criteria						
Any comorbid disorder	80.9 (37.4)	74.9 (35.3)	66.9 (36.9)	7.08	.008	1.008
Conduct disorder	8.1 (25.7)	6.6 (20.7)	6.4 (18.9)	0.52	.47	
Oppositional defiant disorder	23.0 (40.9)	25.2 (37.2)	22.9 (33.0)	0.07	.80	
Any anxiety disorder	42.6 (47.9)	41.4 (41.2)	32.4 (37.5)	3.02	.08	
Panic disorder	5.6 (22.8)	3.2 (13.4)	2.2 (9.9)	4.14	.04	1.011
Substance use disorder	25.2 (43.2)	12.9 (26.1)	6.4 (17.2)	26.06	<.001	1.014
Medication treatment, <sup>a</sup> % of wk receiving medication during follow-up						
Any psychotropic medication	75.8 (42.3)	81.3 (32.5)	73.1 (34.1)	0.30	.59	
Antimanic	62.3 (47.2)	68.6 (40.3)	60.2 (39.4)	0.17	.68	
Antidepressant	27.0 (42.7)	23.6 (35.7)	19.1 (31.3)	2.55	.11	
Stimulant	23.3 (40.8)	23.3 (39.3)	23.8 (36.7)	0.08	.78	
Psychosocial treatment, <sup>a</sup> % of wk receiving treatment during follow-up						
Any psychosocial treatment	51.7 (41.0)	55.4 (32.6)	42.2 (29.6)	4.71	.03	1.006
Inpatient or residential treatment	11.0 (23.9)	10.0 (22.3)	4.4 (11.6)	6.15	.01	1.010
Specialized psychosocial services	14.5 (34.3)	16.4 (28.6)	13.9 (24.3)	0.05	.83	
Outpatient services	40.7 (38.0)	43.1 (29.7)	30.9 (24.6)	6.45	.01	1.008

<sup>a</sup>The percentage of weeks are derived from Adolescent Longitudinal Interval Follow-up Examination (A-LIFE) ratings; values range from 0% to 100%.

<sup>b</sup>For analyses examining A-LIFE Psychiatric Status Rating (PSR) scores, values range from 1 to 6.

cents with bipolar I disorder (mean age, 16 years) over a 5-year follow-up. Among community adolescents followed up for 4 years into young adulthood (age range, 19-23 years), Lewinsohn and colleagues<sup>43</sup> reported that 5.9% of adolescents with bipolar I or II disorder and 6.3% of adolescents with subthreshold bipolar disorder attempted suicide. The mean age of the COBY sample at study intake was 12.6 years; thus, even followed up longitudinally over 5 years, many COBY youth have yet to pass through the highest risk period for new onset of suicidal behavior (age range, 16-18 years).<sup>44</sup> We therefore expect greater rates of suicidal behavior as the sample ages into young adulthood.

Prior findings that more than 70% of suicide attempts among individuals with bipolar disorder occur during depressive episodes<sup>45</sup> converge with the prominence of depression-related variables in the present study. First, severity of depressive episode at study intake predicted risk for suicidal behavior during follow-up in our sample. Depression at study intake has similarly been as-

sociated with prospective risk for suicidal behavior among adults with bipolar disorder.<sup>4,16</sup> Family history of depression also emerged as a significant predictor of a prospective suicide attempt. Studies of adolescent suicide completers document the substantial contribution of parental depression to offspring suicide risk,<sup>46</sup> even after accounting for the child's depressive severity.<sup>47</sup> It is possible that familial depression contributes to offspring suicide risk via multiple avenues, including decreased familial support and increased conflict.<sup>48</sup> Finally, univariate analyses indicated that subjects who attempted suicide during follow-up were more likely to have past exposure to an antidepressant; this relationship was not significant in multivariate analysis. This finding may be linked to the knowledge that depressive severity is a potent risk factor for suicidality among youth.<sup>49</sup> Thus, those COBY youth with more severe depressive presentations (and therefore also at greater risk of suicide) may have been more likely to be prescribed antidepressants. It is important to note that antidepressant use during follow-up was

not temporally associated with increased suicide risk in this sample, further suggesting that the association is not causal. Similarly, in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study of adults with bipolar disorder,<sup>16</sup> antidepressant exposure was not associated with prospectively examined new-onset suicidal ideation and behavior.

This analysis represents a novel contribution to the literature owing to our ability to identify factors in close temporal proximity (ie, within 8 weeks) to suicide attempts in this population. The identification of near-term risk factors holds importance for informing risk assessment and prevention efforts. We found that more weeks with threshold depression in the preceding 8 weeks was associated with a greater prospective suicide risk. Among adults with bipolar disorder in the STEP-BD study,<sup>16</sup> the percentage of days that an individual was depressed during the year preceding study intake was associated with attempted and completed suicide during 2-year follow-up.<sup>2</sup> As compared with the STEP-BD study,<sup>16</sup> we analyzed prospective factors preceding suicidal behavior using a substantially narrower time frame (ie, 8 weeks); we may conclude with greater precision that depressive burden confers near-term risk.

Retrospective and cross-sectional data support an association between mixed mood states and suicide risk.<sup>21,50,51</sup> In fact, some such studies indicate that suicide attempt rates among adults with bipolar disorder are highest (up to 70%) during mixed episodes.<sup>52,53</sup> In a prospective study of adults with bipolar disorder, Valtonen et al<sup>10</sup> documented a 37-fold elevated risk for a suicide attempt during mixed mood states. To our knowledge, this is the first report to document a proximal temporal association between prospectively examined mixed states and suicide risk among youth with bipolar disorder. We found that a greater amount of time spent with mixed symptoms in the preceding 8 weeks conferred a greater risk for a suicide attempt. Clinical risk assessment of youth with bipolar disorder should attend not only to severity but also to the pervasiveness of acute mixed symptoms.

An association between comorbid substance use disorder and suicide risk in bipolar disorder is well established,<sup>54</sup> and the association appears to be particularly strong among younger patients.<sup>55</sup> We found that more weeks with threshold substance use disorder in the preceding 8-week period was associated with a greater risk of suicide attempt. Substance use is hypothesized to increase the risk for attempted suicide both through the negative impact of substance use on mood disorder and by the increased risk of lethal suicidal behavior while under the influence.<sup>1</sup> However, our data indicate low rates of intoxication (5%) during the suicidal act. Future studies may investigate the specific pathways underlying the association between substance use and suicide risk in pediatric bipolar disorder as a means of improving suicide prevention efforts.

We found greater outpatient psychosocial service use in the preceding 8-week period was associated with a greater risk for a subsequent suicide attempt. Greater amount of time in outpatient psychosocial treatment may reflect recognition on the part of the patient, family, and/or treatment providers that more resources were needed to man-

age the patient's illness severity and/or safety. Thus, these youth may have been getting more treatment in response to greater clinical need. This finding also calls attention to the importance of imminent risk assessment among outpatient providers treating youth with bipolar disorder, referral to higher levels of care when warranted, and the need for suicide prevention efforts for this group.

There were limitations to our study. Prospective data on suicide attempts and other follow-up variables (eg, illness status) were gathered longitudinally in the COBY study and were assessed retrospectively at follow-up periods encompassing an average of 9 months. It is possible that conducting assessments more frequently during follow-up, possibly by using ecological momentary assessment methodology, would increase the reliability of the prospective data. Furthermore, it is possible that the 8-week time period that we used for prospective analyses may have been either too broad or too narrow to adequately capture factors associated with suicidal behavior. Future studies should also aim to expand on the association between significant life events and suicidal behavior in this population. In addition, we relied on patient and parent reports of suicidal behavior, and these reports were not corroborated with emergency and/or inpatient service records. The COBY participants were primarily recruited from clinical facilities and thus may not be representative of youth with bipolar disorder who have not sought treatment. Lastly, given that the COBY sample of participants is predominantly white, these findings may not be representative of cultural minority groups because studies identify culturally specific risk factors for suicidal behavior.<sup>56</sup>

In conclusion, these prospective data indicate pediatric bipolar disorder is associated with high rates of suicide attempts. These findings highlight the importance of suicide prevention strategies in youth with bipolar disorder, including frequent and thorough suicide risk assessment and safety planning. Clinicians treating youth with bipolar disorder should attend to intake depressive severity and to family history of depression when considering the prospective risk for suicidal behavior. Persistent depression, mixed presentations, and active substance use disorder may signal imminent suicide risk in youth with bipolar disorder. Risk assessment targeting these clinical factors for youth with bipolar disorder may help to identify those at highest risk and may contribute to the prevention of suicidal behavior in this population.

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